ACTA OBSTETRICIA ET GYNECOLOGICA SCANDINAVICA

Vol XLVI

LUND 1967 BERLINGSKA BOKTRYCKERIET

TABLE OF CONTENTS

VOL. XLVI

A

B

E

F

G

H

I

J

T

U

V

Y

Peltokallio, Veikko, and Peltokallio, Pekka, Acta obst. et gynec. scandinav. 46, 1967

From the Central Hospital of Central Finland (Oskari Herpola) Jyväskylä Finland

TUBERCULOUS HEPATITIS WITH JAUNDICE IN PREGNANCY

BY

VEIKKO PELTOKALLIO AND PEKKA PELTOKALLIO

Jaundice is rare in connection with tuberculous hepatitis. Four cases were reported by Cleve *et al.* 1954. Curry and Alcott (1955) reported 2 cases of their own and were able to find 30 cases in the literature. Of these, 26 had been diagnosed at autopsy 3 at operative laparotomy and one by percutaneous liver biopsy

In miliary tuberculosis tubercles are usually found in the liver (Finckh *et al* 1953) According to Olderhausen *et al.* (1955) this occurs in 74 per cent. Stürper (1954) found in the literature covering a period of more than a hundred years 364 cases of miliary tuberculosis in pregnancy Isolated cases have been reported by e.g Turner (1953) and Miotti (1958) Mehtas (1961) series of 53 pregnant women with active tuberculosis included 2 with miliary tuberculosis.

Our own patient had miliary tuberculous hepatitis and jaundice, and the situation was complicated further by the patient's pregnancy We have not been able to find a corresponding case in the literature.

Case Report

The patient was farmer wif aged 35 who had previously been fairly healthy There was no family history of tuberculosis. The patient had had 4 earlier pregnancies In May 1959, when her fourth pregnancy was in its fifth month, she developed persistent fever and her general condition deteriorated steadily

The patient consulted physicians and tuberculosis centres without the cause of her pyrexia being detected. She was admitted to the Central Hospital of Central Finland in August 959 when her fever and poor condition had persisted for 2 months. At the time of admission the patient was also



Fig 1 a

Fig 1 Liver needle biopsy specimen showing tubercles Magnification a 40: 1 b 80: 1 c 180: 1

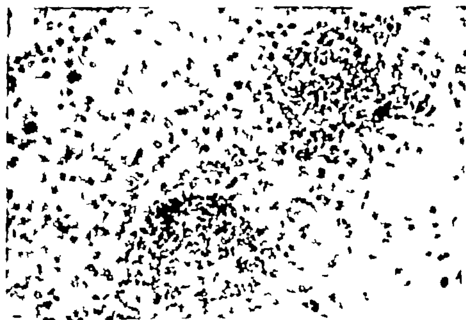


Fig 1 b



Fig

jaundiced On clinical examination slight soft rales were detected and chest roentgenography revealed faint shadowing which was chiefly of miliary type. The liver was palpable 4 finger breadths below the costal arch It was tender The spleen was not felt on palpation. The size of the uterus corresponded to the duration of pregnancy The sedimentation rate was 1 mm/h, the Wasser mann reaction negative, Mantoux 00 negative staining of sputa for tubercle bacilli was negative 3 times and no bacilli grew on culture The Paul-Bunnell test (mononucleosis agglutinins) was negative, Leptospira antibodies were negative, toxoplasma antibodies Sabin-Feldman dye test was negative the complement fixation test was negative. The Vidal test was negative no Plasmodia malariae were seen. L E cells wer not encountered. Alkaline phosphatase was 6 3 King-Armstrong units, SGOT was 79 units SGPT 30 units thymol turbidity test 7 units, Meulengracht test 1. 20, urine tested for iodine gave positive reading,

The patient remained febrile whilst in hospital and the cause could not be detected. Percutaneous liver puncture was performed and histological examination revealed miliary tuberculous hepatitis Drug therapy—streptomycin PAS Rimifon—was instituted immediately the temperature returned to normal within week and the jaundice disappeared The patient was transferred to sanatorium Six weeks after the first liver puncture new specimen was taken and the histological diagnosis was again miliary tuberculous hepatitis Three months after the institution of chemotherapy the patient was delivered of healthy girl, weight 3300 g At delivery samples wer taken from the



Fig. 1 a

Fig. 1. Liver needle biopsy specimen showing tubercles. Magnification. a 40:1 b 80:1 c 180:1

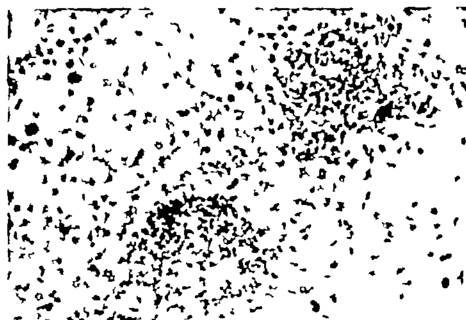


Fig. 1 b

is infected (Jones, 1951) White (1938) described a case in which infection had obviously occurred via the placenta. In our case the child was born healthy and no signs of tuberculosis have been seen in her since. A relatively early diagnosis and consequent effective antituberculosis treatment of the mother obviously gave protection to the child as well when the placenta itself was infected.

SUMMARY

The authors report a very rare case, for they could find no parallel in the literature. A woman who had had fever for 2 months became jaundiced in the sixth month of pregnancy. Percutaneous liver puncture revealed that miliary involvement of the liver by tubercles was the cause of the jaundice.

Immediate antituberculous chemotherapy led to rapid improvement of the mother's condition and her child was delivered normally. Tubercle bacilli were cultured from a placental sample taken at delivery.

Antituberculous therapy of the mother and isolation of the child resulted in both of them being healthy and symptom-free 4 years later.

The authors stress the importance of liver biopsy as an aid to diagnosis in cases of fever of unknown origin. It must be regarded as the saving measure in the present case. Even when there is invasion by miliary tubercles, pregnancy can be brought to a successful conclusion in the present era of antituberculosis drugs.

REFERENCES

Cleve E A Gibson J R., and Webb W M Ann. Int. Med. 4 25 1954
Curry F J and Alcott D Gastroenterology 28 037 955
Froehh E. S. Baker J S and Ryan M. M. P M. J. Australia 2, 369, 953
Goodman R. H and Kessler M D New England J Med. 246 572, 952
Gray N J and Taft L. I M. J Australia I 79, 959
Hammerli U P and Siebenmann R. E Schweiz. Z Tuberk. 17 297 960
Healey R. J Leff A. H and Rosenak B. D Am. J Digest Dis. 4 698 959
Jones J M., M. Clin North Amer 35, 647 951
Lincoln, E. M. and Sewell E. M., Tuberculosis in Children, The Blakiston Division Mc Graw-Hill Book Co., New York 963

placenta for culture for tubercle bacilli and they proved to be positive. The patient s condition improved rapidly during chemotherapy She gained 10 kg in weight her sedimentation rate fell from 102 to 7 mm/h. Drug therapy was continued for 16 months in all The patient made a complete recovery and 5 years later was taken off the register of the Tuberculosis Office The baby was sent immediately after delivery to a children s home for 9 months. She has subsequently been at home and is now aged 4 healthy and well developed.

Discussion

Hepatic tuberculosis is not easy to diagnose Obscure fever enlarged liver and pain under the right costal arch are the most typical symptoms Very frequently the spleen is also enlarged. In our own case the situation was complicated further by the patient s pregnancy The various possibilities of complication due to pregnancy led to erroneous thinking Percutaneous liver biopsy proved the saving measure for out patient with long standing fever poor condition and jaundice As the tubercles are generally spread diffusely throughout the liver percutaneous puncture is a rewarding measure Cases of miliary tuberculosis diagnosed by liver puncture have been reported by Healey *et al* (1959) Gray and Taft (1959) and Haemmerli and Siebenmann (1960) Jaundice as a symptom of tuberculosis is very rare Its cause may be extrahepatic in which case the tuberculosis gland constricts the biliary passages or intrahepatic caused by cellular damage as in our case

According to Stürper (1954) miliary tuberculosis as a com plication of pregnancy is generally encountered in the puerperium. The majority of the cases occur during the first or second preg nancy Our own case involved the fifth pregnancy and the miliary involvement of the liver appeared in a fairly early phase of the pregnancy In spite of anti tuberculosis therapy for 3 months tubercle bacilli were grown from the placenta after delivery Placental tuberculosis is uncommon Schaefer (1939) studied the placenta of 150 women with tuberculosis and detected it in only one placenta An isolated case of tuberculosis of the placenta was published by Goodvin in 1952 The child is infected very rarely via the placenta during the foetal period (Lincoln 1963) except in cases in which the placenta also

Gad, Claus, Acta obst. et gynec. scandinav. 46, 7 1967

From the Department of Gynecology and Obstetrics (P. Stougaard-Andresen) the Central Hospital Esbjerg, Denmark

PARACERVICAL BLOCK

A 30 months report

BY

CLAUS GAD

Paracervical block for local anesthesia in the first stage of labour was used in France and Germany as far back as in 1926 but does not appear to be very popular in these countries to-day On the other hand the method is used with increasing frequency in the U.S.A. In 1945 Rosenfeldt described the successful use of paracervical block in 100 cases. Chassar Moir (1965) found the method extremely useful and free from risk. Nearly all articles give similar favourable evaluations of the method. Two double blind trials have been reported (Pitkin and Goddard 1963 Seeds *et al.* 1962) and these comprised 100 and 268 cases respectively Injection of local anesthetic solution had an excellent effect in approximately 80 per cent of the cases in both series, a poor effect in 5.6 per cent of the cases in one series and in 16 per cent of the cases in the other series When saline only was injected a good effect was obtained in only 12 and 24 per cent of the cases respectively There was no cases of foetal asphyxia or death (apart from a neonatal death resulting from extensive malformations) There is only one report which questions the safety of the method (Nyirjesy *et al.* 1963) In this series of 68 patients there was significant variation in the foetal heart rate in 15 cases and one foetal death was assumed to result from paracervical block.

Opinions on the effect of paracervical block on the uterine contractions are contradictory (Baken *et al.* 1962 Nyirjesy

Mehta B R. Dis Chest 39 505 1961
Miotti T Friuli med. 13 327 1958
von Olderhausen H F von Olderhausen R. and *Tellesz A.* Klin. Wchnschr 33 104 1955
Schaefer G Am J Obst. & Gynec. 138 1066 1939
Stürper P Arch Gynäk. 185 359 1954
Turner H G jr Am. Rev Tuberc. 68 253 1953
White G M and *Porter D F* Canad. M. A. J 39 165 1938

Received on April 24th 1968

by vaginal exploration, and a tubular guide 14.8 cm long is held against this area. When the needle is introduced via the guide tube it enters the tissue to maximum depth of 7 mm. The same set of instruments is employed for pudendal nerve block which is used routinely in the second stage of labour in this department.

The paracervical block is placed in the lateral fornix close to the uterus. With cervical dilatation of 5 cm or less the injections are placed at 3 and 9 o'clock, with greater dilatation the injections are placed increasingly posterior as, with advanced dilatation, the parametria are displaced backwards. Owing to the extensive venous plexuses in the area frequent aspiration is advisable.

A % solution of Carbocain[1] was used as the anaesthetic agent as it is only slightly toxic and has a protracted effect. Initially 1 ml was used on each side; later the dose was reduced to 5 ml. The blocks were carried out by the house surgeons or students employed in the department at the time.

Observations were carried out and forms filled in by the patient's own midwife, who attends the patient while in the department as no permanent midwives are attached to the department. The recordings are based entirely upon the judgement of the midwife which is in turn based upon her observation and information from the patient. The observations are recorded on pro forma detailing the following: the analgesic effect of the block, the strength, the frequency and duration of the uterine contractions, the dilatation of the cervix and the foetal heart rate which, according to custom, is taken for 3 consecutive 5 second periods. These results are noted every 5 minutes for the first 30 minutes and every half hour thereafter. The effect of the block is judged either as "good" which denotes total or almost total cessation of the pain, or "fair" which denotes reduction in the pain, but with persistence of certain amount of pain, or "poor" with slight or no reduction of the pain. The observations taken at 0, 30, 30, 60 and 90 minutes only have been included in the review. As the time of change from one category of effectiveness to another has not been noted, a block that at the end of 30 minutes was noted as "good" and at 60 minutes had ceased worked well between 30 and 60 minutes and not necessarily for only 30 minutes.

Results

The results are mainly based upon individual assessment. The pain intensity is without doubt very different for different patients and various women react differently to pain of the same intensity. The criteria of evaluation of the different midwives *undoubtedly* varies also. In addition the effect of the block must of necessity be related to the intensity of the pain at the time the block was carried out. If the patient states that there is no difference in the

[1] Carbocain BOFORS (Mepivacaini chloridum NFN)

et al. 1963 Pitkin and Goddard, 1963 and Zourlas and Kumar 1965) Some investigators have demonstrated a reduction in the strength of the contractions as measured by tocography but at the same time progression of cervical dilatation is unchanged. Others consider that they have demonstrated an acceleration in the dilatation

Apart from a periodical occurrence of a slower fœtal heart rate following paracervical block the main argument against the use of the method has been its time limit. Baggish (1964) has attempted to avoid this limitation by using a continuous paracervical block, inasmuch he inserted via the perineum into the paracervical tissue a teflon catheter through which he gave periodic injections Delivery was conducted with the catheter in place. The results were excellent but the main advantage of paracervical block its simplicity is lost.

Material

There were 2963 births in the Obstetrical Department of the Sct. Joseph s hospital in Esbjerg during the period 1/10 1962–31/3 1965 Paracervical block was used in the first stage of labour in 1716 patients. In 213 cases or 12.4 per cent the procedure was repeated making a total of 1929 paracervical blocks In order to obtain a certain minimum observation time 149 cases in which the birth took place within the first 45 minutes after the block had been given were excluded from the review A further 77 cases were excluded owing to insufficient records. Thus 1703 paracervical blocks are included in the final analysis The work is a retrospective study the aim of which has been to evaluate the method when used in practice in special department.

Method

The method depends upon injection of a local anaesthetic agent into the pelvic plexuses located lateral to the uterine cervix at the root of the parametrium. Pain sensations are transmitted to these plexuses via the sympathetic nerves which pass along the branches of the uterine arteries.

For the injection a 16.5 cm long hypodermic needle mounted upon an ordinary hypodermic syringe is used. The desired site for injection is localized

dilatation of more than 5 cm form the borderline groups. In these groups good effects were obtained in 79 2 per cent and 70.9 per cent respectively fair in 14.8 per cent and 20.6 per cent, and poor in 6 per cent and 8 5 per cent. But the smaller number of blocks with good effect is counteracted to a certain degree by a higher proportion with fair effect. These very small variations can quite possibly be explained by purely anatomical and technical factors. The anatomy is well-defined in the primigravidae and together with the slight degree of cervical dilatation this can be considered to help in the correct positioning of the anaesthetic agent.

There were slight variations between the two periods when dif ferent doses of Carbocain were used (Period I 1 % 10 ml.×2 Period II 1 % 5 ml×2) Thus in primigravidae with cervical dilatation of less than 5 cm the results were as follows Period I — good 76.9 % fair 15.9 % poor 7 2 % Period II — good 80.8 % fair 14 0 % poor 5.1 % Similar figures are found when other groups in the two periods are compared. Thus it seems certain that halving of the dose did not reduce the effectiveness of the block.

Figure 1 shows the percentage distribution according to the duration of the 1262 nerve blocks which resulted in a good" effect and the same for the 1580 blocks that resulted in a good" and/or fair effect. It can be seen from this that in those cases with good effect the duration of effect was more than 60 minutes in 15.9 per cent, and more than 30 minutes in 62 7 per cent. The corresponding figures for the good" and/or fair effects are 34.8 per cent and 80.4 per cent. In the various subgroups primigravidae and patients early in labour obtained the longest effects. This is to be expected as these patients obtain a slightly better initial effect and have a longer labour than other patients. As already mentioned 149 blocks (7 7 per cent) have been excluded owing to the fact that the birth took place 45 minutes or less from the time the block was established. But a large number of births which are included in the material took place 45–90 minutes after the block was established and such blocks therefore could not always be tabulated during their full duration. In the second stage of labour the character of the uterine contractions change and as the patient becomes almost free from pain, it is therefore difficult

Table I *The Primary Analgesic Effect in the Various Age Groups and for the Whole Series.*

Age	Effect No	Good No	%	Fair No	%	Poor No	%
under 20	366	267	72.9	69	18.9	30	8.2
20–29	1080	806	74 6	204	18 9	70	6 5
over 30	257	189	73.5	45	17 5	23	9.0
total	1703	1262	74 1	318	18 7	123	7 2

intensity of the pain prior to the establishment of the block as compared with half an hour later, this does not exclude the possibility that she obtained some relief inasmuch as without the block she is likely to have had increasing pain This fact will result in an underestimation of the effect of the block. For these reasons it was not considered relevant to carry out more detailed statistical evaluation of the figures.

The results were analysed for the whole series In addition the results were analysed for the age groups under 20 years of age 20–29 years and over 30 for primigravidæ (1067) and multigravidæ (636) for blocks established with cervical dilatation of less than 5 cm (782) and over 5 cm (921) Finally there were two periods where 20 ml (750) and 10 ml (953) of local anæsthetic were used respectively and these have been computed separately

The initial effect of the block was noted followed by the duration and deterioration of the effect Often after an initial good effect the block would continue to have a fair effect for some time.

The initial effect is nearly always evident within a few minutes. Table I shows the effects obtained in the total series and in the age groups. It can be seen from this that a total of 74 1 per cent of the blocks had a good effect, 18 7 per cent fair and 7 2 per cent poor effect There was little deviation from these figures in the various age groups

If the material is analysed in relation to the other variable factors no major differences can be seen The primigravidæ with cervical dilatation of less than 5 cm and the multigravidæ with

dilatation of more than 5 cm form the borderline groups. In these groups good effects were obtained in 79.2 per cent and 70 9 per cent respectively fair in 14.8 per cent and 20 6 per cent, and poor in 6 per cent and 8 5 per cent. But the smaller number of blocks with good effect is counteracted to a certain degree by a higher proportion with fair effect. These very small variations can quite possibly be explained by purely anatomical and technical factors. The anatomy is well-defined in the primigravidæ and together with the slight degree of cervical dilatation this can be considered to help in the correct positioning of the anæsthetic agent.

There were slight variations between the two periods when dif ferent doses of Carbocain were used (Period I 1 % 10 ml.×2 Period II 1 % 5 ml×2) Thus in primigravidæ with cervical dilatation of less than 5 cm the results were as follows Period I — good 76.9 % fair 15.9 % poor 7.2 % Period II — good 80.8 % fair 14.0 % poor 5.1 % Similar figures are found when other groups in the two periods are compared. Thus it seems certain that halving of the dose did not reduce the effectiveness of the block.

Figure 1 shows the percentage distribution according to the duration of the 1262 nerve blocks which resulted in a good" effect and the same for the 1580 blocks that resulted in a good" and/or fair effect. It can be seen from this that in those cases with good effect the duration of effect was more than 60 minutes in 15.9 per cent, and more than 30 minutes in 62.7 per cent. The corresponding figures for the good and/or fair effects are 34.8 per cent and 80.4 per cent. In the various subgroups primigravidæ and patients early in labour obtained the longest effects. This is to be expected as these patients obtain a slightly better initial effect and have a longer labour than other patients. As already mentioned 149 blocks (7 7 per cent) have been excluded owing to the fact that the birth took place 45 minutes or less from the time the block was established. But a large number of births which are included in the material took place 45-90 minutes after the block was established and such blocks therefore could not always be tabulated during their full duration. In the second stage of labour the character of the uterine contractions change and as the patient becomes almost free from pain, it is therefore difficult

Table II. *The Distribution According to the Duration in Minutes of the Effect Given as a Percentage of the Total Blocks in the Groups in Question. The Results are Given for the Whole Series and for Subgroups According to the Parity Dilatation of the Cervix at the Establishment of the Block and the Dose of Local Anaesthetic (Period I Carbocain 1 % 10 ml×2 Period II. Carbocain 1 % 5 ml×2)*

	Good			Good and or Fair		
	No Effect	0—30 Min	30—60 Min or Above	No Effect	0—30 Min	30—60 Min or Above
Primigravidae	[illegible]4.2	25.6	50.1	6 5	15 9	[illegible]7.6
Multigravidae	[illegible]8.6	31 0	40.4	8 3	[illegible]	69 5
Cervical dilatation over 5 cm.	[illegible]8 0	30 1	41 9	[illegible].6	[illegible]0.4	72.0
Cervical dilatation less than 5 cm.	3.4	[illegible]4 7	51.9	6.8	15 6	[illegible]7.6
Period I.	[illegible]7.2	[illegible] 9	44 9	8 5	1 9	3.6
Period II	24 9	[illegible]4	47 7	6 2	18 5	[illegible]5 3
Whole series	[illegible]5 9	[illegible].6	46 5	7.2	18.2	4.6

to evaluate the effects of the block at this time Often the effects were recorded only until the bearing down began So there is little doubt that the values stated can be regarded as the minimum rather than the true duration

In Table II an attempt has been made to give a wider evaluation of the duration of effects as a percentage of the total number of blocks included in the material The same small variations can be seen again and it is worth noting that there appears to be a slightly better effect in the 2nd period where a smaller dose of anaesthetic was used than in the 1st period. The variations probably originate from the slight difference in the primary effect.

Complications

In the discussion on the usefulness of paracervical block the good analgesic effect is universally acknowledged but the risk of harming the child is questioned. Statements constantly appear on the influence of the block on the foetal heart rate in association with a proportion of the blocks. This proportion will naturally depend

upon the criteria used for an abnormal heart rate, as there is no definite division between normal and abnormal. In this series the heart action has been considered affected if the heart rate was 9 or under in any one of the 3 consecutive 5 second periods.

Firstly a summary will be given of the deaths in infants weighing over 2000 g occurring during birth and within the first seven days of life that took place in all the deliveries during the period under study The total was 8 during birth and 16 after *i.e* 24 Of these 6 weighed 2000–2500 g. In 10 cases paracervical block had been established in 14 no block had been used. In 19 cases the main cause of death was malformation (7) prolapse of the umbilical cord (2) strong Rhesus immunization (2) rupture of the uterus (2) abruption of the placenta (2) shoulder presentation (1) mechanical obstruction (1) unknown cause (no heart sounds on admission to hospital during labour) (2) In none of these cases would a paracervical block cause the death of the child. Out of the remaining 5 cases no block was given in 1 case (presumable cause of death cerebral haemorrhage) There are thus 4 deaths in which the block may have played a part. In 3 cases the heart action remained unchanged after the block. In 1 of these the birth was induced by rupture of the membranes owing to suspected placenta insufficiency the child weighed 2200 g and cried immediately developed respiratory distress and died 7½ hours after birth. The second child was delivered by the breech without difficulty The heart rate was affected in the last part of the second stage The child was dysmature (2700 g, 50 cm) The umbilical cord was coiled once around the neck. The child suffered from asphyxia and died 18 minutes later The third child (3100 g, 54 cm) also suffered from asphyxia and died 11 hours after birth. The delivery was spontaneous and the *post mortem* examination showed no abnormality apart from a finger deformity The fourth case will be discussed later

A change in the foetal heart rate after paracervical block was demonstrated in 173 patients and as 9 of these had bradycardia after two blocks, a total of 182 blocks (10.6 per cent) of the total registered blocks resulted in slowing of the foetal heart. In 135 cases (74 per cent) the effect occurred within the first 10 minutes. In 163 cases (89 5 per cent) the effect was of 10 minutes dura

Table II. *The Distribution According to the Duration in Minutes of the Effect Given as a Percentage of the Total Blocks in the Groups in Question. The Results are Given for the Whole Series and for Subgroups According to the Parity Dilatation of the Cervix at the Establishment of the Block and the Dose of Local Anaesthetic (Period I Carbocain 1 % 10 ml×2 Period II Carbocain 1 % 5 ml×2)*

	Good			Good and/or Fair		
	No Effect	0—30 Min	30—60 Min or Abo	No Effect	0—30 Min.	30—60 Min or Abo
Primigravidae	24 2	25.6	50 1	6 5	15 9	77.6
Multigravidae	28.6	31 0	40.4	8.3	22.2	69 5
Cervical dilatation over 5 cm.	28.0	30 1	41.9	6	20.4	72.0
Cervical dilatation less than 5 cm	23.4	24	51.9	6.8	15.6	77.6
Period I.	27.2	27 9	44 9	8 5	17 9	73.6
Period II	24 9	27.4	47 7	6.2	18 5	75 3
Whole series	25 9	27.6	46 5	7.2	18.2	74.6

to evaluate the effects of the block at this time Often the effects were recorded only until the bearing down began So there is little doubt that the values stated can be regarded as the minimum rather than the true duration

In Table II an attempt has been made to give a wider evaluation of the duration of effects as a percentage of the total number of blocks included in the material The same small variations can be seen again and it is worth noting that there appears to be a slightly better effect in the 2nd period where a smaller dose of anaesthetic was used than in the 1st period. The variations probably originate from the slight difference in the primary effect.

Complications

In the discussion on the usefulness of paracervical block the good analgesic effect is universally acknowledged but the risk of harming the child is questioned. Statements constantly appear on the influence of the block on the foetal heart rate in association with a proportion of the blocks This proportion will naturally depend

Among the 9 cases where the infant failed to cry immediately there was 1 death (during delivery) and 4 children were asphyxiated. The children suffering from asphyxia began breathing normally within 1 to 7 minutes and none of them showed any signs of abnormality on discharge. Four infants were only slightly affected with regard to respiration, heart action and muscular tonus. They were quickly resuscitated by oxygen and aspiration. Eight of the mothers were primigravidæ and one a secundigravida.

The case of foetal death is of special interest. The patient was a 28 year old primigravida who had been previously subjected to operation for appendicitis and atoxic goitre. She gave birth at term after uncomplicated pregnancy. After the first paracervical block the foetal heart action remained perfectly normal, and the membranes were ruptured. Ten minutes after the second block the heart rate became slow: first 7–8–8 and 5 minutes later 7–7–7 after which it returned to normal for the following 55 minutes. By this time the os was almost fully dilatated and a pudendal block was established. Immediately afterwards the heart rate fell to 6–6–6 and did not return to normal despite the use of oxygen. The child was delivered by vacuum extraction 25 minutes after the pudendal block in a normal occipital presentation. Heart sounds were present but ceased after 25 minutes during which resuscitation using oxygen aspiration and stomach aspiration was attempted. No respiration was present. The birth weight was 3700 g. The *post mortem* examination showed nothing but complete atelectasis. The fact that the paracervical blocks could possibly have contributed to this death cannot be refuted but it seems unlikely. The effect on heart beat was short and the bradycardia moderate. When the heart rate was again affected after approximately 1 hour this took place during the second stage. Vacuum extraction was quickly carried out and heart action was present at birth.

With regard to the 8 children who showed some signs of asphyxia the relationship with the block is very flimsy in the 5 cases in which the birth took place several hours later. Two of these children were delivered by vacuum extractor owing to bradycardia during the second stage (one was a large child with impacted shoulders). One child was delivered by the breech, one

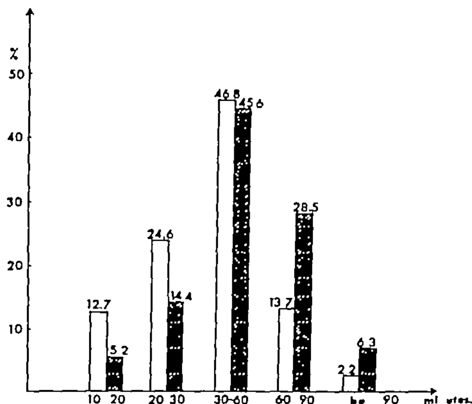


Fig. 1. The percentage distribution of the blocks according to the duration in minutes. White columns — blocks with "good" effect. Shaded columns — blocks with "good" and/or "fair" effect.

tion or less. Only in one case was the slowing as much as 4 per 5 seconds but a total of 8.7 per cent cases showed a maximum depression of 5 per 5 seconds. The remaining cases were distributed almost equally between 6 to 9 per 5 seconds.

In the 173 deliveries 164 children cried immediately after birth. In four of these cases the foetal bradycardia required operative delivery: 3 were delivered by vacuum extractor and the last by Cesarean section. In addition to the bradycardia there was meconium stained amniotic fluid in two of these cases. One of the four children had had a slow heart action during the whole delivery (5–6–5) and the heart action remained at the same level after birth. The child was later found to have an atrio-ventricular block. None of the remaining 163 children showed any abnormality on discharge.

No attempt has been made to measure the effect of the block upon the uterine muscles or the progression of the birth. It is reasonable to claim that the patient, who has been free from pain immediately prior to the second stage has been relaxed and possibly been asleep an hour or so will be less exhausted than the patient, who during the same time has been subjected to considerable pain. This presumably makes the second stage more effective and thus shortens it.

The intention in reducing the dose to 5 ml×2 of a 1 % solution of carbocain was to allow the procedure to be repeated. After the reduction of the dose the block was repeated in 15.7 per cent of the cases against 8 6 per cent previously No definite changes in the frequency of bradycardia in the foetus occurred inasmuch as this was 11.2 per cent in the first and 10 3 per cent in the second period.

Conclusion

The present study of the effects of paracervical block shows as do many previous studies that the method is eminently suitable for reducing the pain late in the first stage of labour If the block ceases to be effective before it is desired, then it can be repeated. A reduction in the dosage from 10 ml×2 to 5 ml×2 of Carbocain 1 % has no influence on the effect. The method is technically simple and painless. Foetal bradycardia which is often mentioned as a complication also occurred in this series but a connection between this and asphyxia and foetal death must on the present evidence be considered unlikely

SUMMARY

A retrospective report is given on 1703 paracervical blocks given late in the first stage of labour in a special department during a period of 2½ years. The character of the study based upon assessment by midwives is emphasized. The average pain relieving effect was termed good" fair and poor in 74.1 18 7 and 7.2 per cent of the cases respectively The good effect obtained lasted 30–60 minutes or longer in 62 7 per cent, whilst the effect

had an unaffected heart action after the second block despite an affected heart action after the first. Finally one was delivered in an occiput posterior position and was only slightly affected at birth In one of the 3 last mentioned cases the effect on the heart rate came very late and at the beginning of the second stage the child was delivered by vacuum extraction In another case continuous contraction of the uterus took place as the bradycardia began The last child was delivered by vacuum extraction 50 minutes after the block had been established. The block was thus established approximately at the beginning of the second stage. The umbilical cord was tightly coiled around the neck and one shoulder The child had spasms in the right limbs for the first 24 hours and for a further 24 hours lay in opisthotonus with poor respiration It recovered after this and was completely normal during the remaining time in hospital, *i.e* till the seventh day after birth. The connection with the paracervical block does not appear to be well established in this case but cannot be excluded. No follow-up of the children was carried out.

No maternal complication were observed.

Other factors

The patients included in the series are not representative of the clientele from the department. It can be seen that only 1716 of the 2963 (58 per cent) of the obstetric patients were subjected to paracervical block despite the fact that this is a routine procedure This can be explained partly by the fact that a large number of patients are admitted at a late stage of labour and, to a lesser degree, by the fact that a certain number of deliveries in a special department are operative ones. It is obvious that the group which avoids paracervical block includes the majority of multi gravidæ as these give birth in the shortest time. Therefore the primigravidæ dominate the series.

The technique of the block is very simple and new staff can after short instruction obtain results similar to those with more experience The large majority of the patients state that the injections are free from pain The procedure thus only involves with the usual inconvenience associated with vaginal examination

Skjødt Preben, Acta obst. et gynec. scandinav. 46, 19, 67

From the State Maternity Hospital Aarhus (Professor M. Ingerslev) and the Blood Group Laboratory (F Kissmeyer-Nielsen M.D.) the Municipal Hospital Aarhus, Denmark

ACTIVATION OF THROMBOPLASTIN IN A CASE OF ABRUPTIO PLACENTÆ WITH HYPOFIBRINOGENEMIA

BY

PREBEN SKJØDT

In a previously published paper on premature separation of the placenta an associated severe coagulation defect was found to be due to a marked increase in the fibrinolytic activity of the blood. This increased activity may have been secondary to intravascular coagulation or possibly provoked by shock. The formed plasmin further aggravated the coagulation status by decomposition of fibrinogen and other coagulation factors. As a result, a haemorrhagic diathesis developed with profuse bleeding from a well-contracted uterus, bleeding from the sites of venupuncture, petechiæ and hæmaturia (Albrechtsen and Skjødt, 1962)

In another previously mentioned case of premature separation of the placenta with hæmorrhagic diathesis before delivery severe respiratory symptoms during the infusion of human fibrinogen indicated that the coagulation defect was due to intravascular coagulation with secondary fibrinolysis (Albrechtsen and Skjødt, 1964)

With the analytical methods hitherto employed by the author it has not been possible to demonstrate directly intravascular activation of the coagulation process. The introduction of the thromboplastin activation test as described by Astrup and Ollendorff (1961) should facilitate the study of these conditions.

A case of premature separation of the placenta where extensive retroplacental coagulation seems to be the essential cause of the serious coagulation defect is now reported. The results of the

"good" and/or "fair" was for the same duration in 80.4 per cent. In 12.4 per cent of the cases the block was repeated. A transient bradycardia occurred in 10 6 per cent of the cases. In this group out of 173 children there were 1 death, 4 with asphyxia and 4 slightly affected. The last 8 cases were completely healthy on discharge 7 days later A possible causual effect of the para cervical block in these cases is discussed.

REFERENCES

Baggish M. S Am. J Obst. & Gynec. 88 968 1964
Baken M. P *Freemann* D N., and *Barno* A. Gynecology & Obstetrics 114 375 1962
Chassar Moir J Triangle 7 1.8 1965
Nyirjesy I *Hawks* B. L. *Hebert* J E. *Hopwood*, H G and *Falls* H C. Am. J Obst. & Gynec. 87 31 1963
Pitkin R. M and *Goddard* W B Obst. & Gynec. 21 737 1953
Seeds A. E. *Stein Messinger* P and *Dorsey* J H., Obst. & Gynec. 20 462, 1962
Zourlas P A. and *Kumar* D Am. J Obst. & Gynec. 91 17 1965

Received on April 25th 1966

Skjødt, Preben, Acta obst. et gynec. scandinav. 45, 19, 1967

From the State Maternity Hospital, Aarhus (Professor M. Ingerslev) and the Blood Group Laboratory (F. Kissmeyer-Nielsen, M.D.) the Municipal Hospital, Aarhus, Denmark

ACTIVATION OF THROMBOPLASTIN IN A CASE OF ABRUPTIO PLACENTÆ WITH HYPOFIBRINOGENEMIA

BY

PREBEN SKJØDT

In a previously published paper on premature separation of the placenta an associated severe coagulation defect was found to be due to a marked increase in the fibrinolytic activity of the blood. This increased activity may have been secondary to intravascular coagulation or possibly provoked by shock. The formed plasmin further aggravated the coagulation status by decomposition of fibrinogen and other coagulation factors. As a result, a hæmorrhagic diathesis developed with profuse bleeding from a well-contracted uterus, bleeding from the sites of venipuncture, petechiæ and hæmaturia (Albrechtsen and Skjødt, 1962)

In another previously mentioned case of premature separation of the placenta with hemorrhagic diathesis before delivery severe respiratory symptoms during the infusion of human fibrinogen indicated that the coagulation defect was due to intravascular coagulation with secondary fibrinolysis (Albrechtsen and Skjødt, 1964)

With the analytical methods hitherto employed by the author it has not been possible to demonstrate directly intravascular activation of the coagulation process. The introduction of the thromboplastin activation test as described by Astrup and Ollendorff (1961) should facilitate the study of these conditions.

A case of premature separation of the placenta where extensive retroplacental coagulation seems to be the essential cause of the serious coagulation defect is now reported. The results of the

thromboplastin activation test according to Astrup and Ollendorff (1961) indicated the presence of clot promoting components in the peripheral blood. These components may possibly have originated from the reflux of serum from the retroplacental haematoma to the maternal circulation (Wessler 1955 Nilsen 1963) but they may also have been due to intravascular activation of the coagulation process

Case Report

J.no 985/63–64 29-year-old gravida V para IV with expected date of confinement January 1964 The pregnancy progressed normally apart from a slight tendency to oedema. There was neither proteinuria nor hypertension.

On the *3rd of Oct* 1963 at 6 00 p.m. the patient had a sudden onset of of loin pain diffuse abdominal pain and diarrhoea. She had blurred vision and was dizzy but had no respiratory embarrassment.

At 8 00 p.m. fresh vaginal bleeding occurred and at 9.30 p.m. she was admitted to the State Maternity Hospital Aarhus. The patient was pale and in pain but not shocked the blood pressure was 115/70 and the pulse rate 84 and of good volume The tense and tender uterus reached 2 cm above the umbilicus The venous blood coagulated spontaneously in ten minutes with formation of a large clot.

At 11 00 p.m there were regular contractions. Blood pressure and pulse rate were unchanged. By now the total blood loss amounted to 300 ml and slight vaginal bleeding continued. At vaginal examination the cervix was found to admit one finger the foetus presented by the breech. After rupture of the membranes blood-stained amniotic fluid was discharged.

At 11 30 p.m. a very frail clot was formed by addition of thrombin to plasma. This indicates lack of fibrinogen if no antithrombin is present. After further addition of bovine fibrinogen a solid clot formed This was kept at 37 C for observation of fibrinolysis. Incipient dissolution of the clot was noted after 30 minutes and in three hours the clot had disappeared.

At 11.45 p.m. the patient s condition was unchanged. The uterus had clearly enlarged and now reached 5 cm above the umbilicus. The first blood transfusion (1) was begun.

On *Oct 4* at 0 15 and 2.00 a m. rapid analyses still indicated lack of fibrinogen and also disclosed increased fibrinolysis (beginning after one hour and complete after three hours) The blood pressure was about 115/70 and the pulse rate 80 and of good volume There was no dyspnoea and no cyanosis. The uterus was very tense and tender and there was continued discharge of blood-stained amniotic fluid.

At 2.45 a.m. another transfusion (2) was administered.

At 4 00 a.m the patient s condition was unchanged and she was still in

pain despite the administration of 75 mg of pethidine. There was no dyspnoea or cyanosis. The uterus was tense and tender. There was no bleeding from the sites of venepuncture and no ecchymoses were present. The urine was clear; microscopy revealed no erythrocytes. Rapid analyses still indicated lack of fibrinogen but by now there were no signs of increased fibrinolysis.

At 5.00 m. the vaginal bleeding increased. The total loss of blood was estimated at 800 ml. The patient seemed to be in less pain, but the uterus was still tense. The blood pressure was about 120/80 and the pulse 95. The cervix still admitted one finger 50 mg of pethidin was administered together with a further blood transfusion (3). As labour failed to progress an oxytocin infusion was started (0 1 u./ 000 ml 5 % glucose)

At 6 30 a.m. the contractions increased and there was intermittent discharge of non-coagulated blood from the vagina. The blood pressure and the pulse rate were unchanged.

At 7.05 m. another blood transfusion (4) was commenced.

At 8.00 a.m. there was still slight vaginal bleeding and very marked tension of the uterus. There was no dyspnoea or cyanosis. The blood pressure was 35/85 A fibrinogen concentration of 60 mg/ 00 ml was now measured and there were no signs of increased fibrinolytic activity

At 9.00 a.m. the total loss of blood was estimated at 100 ml. The patient was restless and in pain. The cervix was fully dilated and a further blood transfusion (5) was commenced.

At 9.10 m. female abortion, weight 800 g, was delivered by traction on foot. Immediately after this the placenta was delivered. It was small and completely flattened and free from infarcts. At the same time large solid clot was discharged together with some liquid blood, total 1200 ml. The fibrinogen concentration was 70 mg/ 00 ml. The uterus contracted well during continued infusion of oxytocin.

At 9 25 a.m. infusion of human fibrinogen (6 g in 300 ml saline 9 %) was commenced to correct the hypofibrinogenemia and to combat the bleeding which continued in spite of the fact that the uterus was well-contracted

At 00 m the fibrinogen infusion was completed. There had been no complications during this and in particular no dyspnoea or cyanosis. The fibrinogen concentration rose to mg/100 ml. The blood pressure was 0/70 and the pulse rate 85

At 10 30 m there was continued bleeding, despite normal uterine tone and so another 6 g of human fibrinogen was administered

At 30 m the bleeding had practically stopped. The total loss of blood amounted to 2500 ml. The patient's general condition was satisfactory and the uterus was well-contracted. The blood pressure was 25/75, the pulse rate 9 By catheterization 300 ml clear urine was obtained There was proteinuria (4 g/litre).

After three days the proteinuria had cleared The puerperium was otherwise without complications The daily urinary output was about 000 ml and the specific gravity 16 Temperature, pulse rate and blood pressure

were normal HB was estimated to 75 % on the 7th day during the puerperium. The patient had no complaints when she was discharged one week after the delivery

Coagulation Analyses

Coagulation analysis for rapid determination of the fibrinogen content and of the fibrinolysis was performed by adding 0.2 ml thrombin ROCHE (20 NIH/ml) to a mixture of 0.2 ml undiluted plasma and 0.2 ml veronal buffer pH 7.4 If the fibrinogen content is sufficient and no anti thrombin is present a clot will be formed. This is incubated at 37 C for observation of fibrinolysis. Normally this kind of clot is not dissolved within the first 24 hours. If clot formation failed or was insufficient the veronal buffer was replaced by 0.2 ml bovine fibrinogen 400 mg/100 ml, and the test was repeated.

The procedure for the drawing and preparation of blood samples was as previously described (Skjodt and Albrechtsen, 1965) The methods for the determination of hæmatocrit, platelet count recalcification time thromboplastin activation test (Astrup and Ollendorff 1961) the thromboplastin generation screening test (Hicks and Pitney 1957) the prothrombin—proconvertin (P P) factor V prothrombin and thrombin times the determination of fibrinogen measurement of fibrinolytic activity in plasma and in iso-electrically precipitated plasma (euglobulins) on standard fibrin plates and on heated fibrin plates and plasminogen determination have also been described previously (Skjodt and Albrechtsen 1965)

A detailed description is given only of the thromboplastin activation test according to Astrup and Ollendorff (1961) This analysis is an indication of the formation of plasma thromboplastin and of thrombin in plasma after recalcification Principally the technical procedure consists of repeated additions at intervals of one min in a period of 14 minutes of a small amount of the recalcified incubation mixture containing patient plasma to a series of test tubes with platelet poor human substrate plasma The coagulation times in the test tubes are recorded and the recalcification time in the incubation mixture is measured. In a

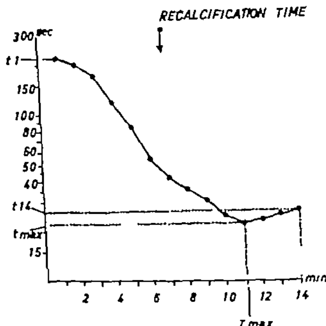


Fig. TAT on normal, platelet-rich human plasma (platelet count 398,000/mml) Plasma 25 ml+0.25 ml 0.0083 molar $CaCl_2$ in ml veronal buffer pH 7.4. The arrow indicates the recalcification time.

normal person the coagulation times will shorten gradually due to increasing amounts of plasma thromboplastin and thrombin. The results are plotted on a graph with the time in minutes as the abscissa and the logarithm of the coagulation times measured in seconds as the ordinate A normal curve is shown in Fig. 1 It may be characterized by the values t 1 t max, T max, t 14 and the recalcification time in the incubation mixture as previously described (Skjodt and Albrechtsen 1965)

The changes in the course of the TAT curves occur by varia tions in the platelet count and in the concentration of the coagula tion factors. The presence of clot promoting components such as serum and tissue thromboplastin may also change the curve As these components possibly may be found following premature separation of the placenta the form of the TAT curves when the coagulation process of the blood has been activated and when

were normal. HB was estimated to 75 % on the 7th day during the puerperium. The patient had no complaints when she was discharged one week after the delivery.

Coagulation Analyses

Coagulation analysis for rapid determination of the fibrinogen content and of the fibrinolysis was performed by adding 0.2 ml thrombin ROCHE (20 NIH/ml) to a mixture of 0.2 ml undiluted plasma and 0.2 ml veronal buffer pH 7.4. If the fibrinogen content is sufficient and no anti thrombin is present a clot will be formed. This is incubated at 37 C for observation of fibrinolysis. Normally this kind of clot is not dissolved within the first 24 hours. If clot formation failed or was insufficient the veronal buffer was replaced by 0.2 ml bovine fibrinogen 400 mg/100 ml, and the *test was repeated*.

The procedure for the drawing and preparation of blood samples was as previously described (Skjødt and Albrechtsen 1965). The methods for the determination of hæmatocrit, platelet count, recalcification time, thromboplastin activation test (Astrup and Ollendorff 1961), the thromboplastin generation screening test (Hicks and Pitney 1957), the prothrombin—proconvertin (P P), factor V, prothrombin and thrombin times, the determination of fibrinogen, measurement of fibrinolytic activity in plasma and in iso-electrically precipitated plasma (euglobulins) on standard fibrin plates and on heated fibrin plates and plasminogen determination have also been described previously (Skjødt and Albrechtsen 1965).

A detailed description is given only of the thromboplastin activation test according to Astrup and Ollendorff (1961). This analysis is an indication of the formation of plasma thromboplastin *and of thrombin in plasma after recalcification*. Principally the technical procedure consists of repeated additions at intervals of one min in a period of 14 minutes of a small amount of the recalcified incubation mixture containing patient plasma to a series of test tubes with platelet-poor human substrate plasma. The coagulation times in the test tubes are recorded and the recalcification time in the incubation mixture is measured. In a

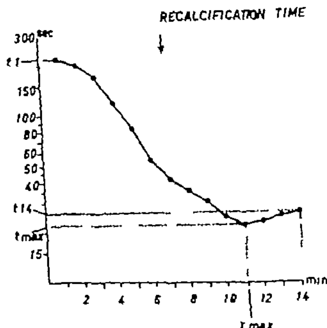


Fig TAT on normal platelet-rich, human plasma (platelet count 398,000/mm³) Plasma 0.25 ml + 0.25 ml 0.083 molar $CaCl_2$ in 2 ml veronal buffer pH 7.4. The arrow indicates the recalcification time

normal person the coagulation times will shorten gradually due to increasing amounts of plasma thromboplastin and thrombin. The results are plotted on a graph with the time in minutes as the abscissa and the logarithm of the coagulation times measured in seconds as the ordinate. A normal curve is shown in Fig 1 It may be characterized by the values t 1 t max, T max, t 14 and the recalcification time in the incubation mixture as previously described (Skjodt and Albrechtsen, 1965)

The changes in the course of the TAT curves occur by variations in the platelet count and in the concentration of the coagulation factors. The presence of clot-promoting components such as serum and tissue thromboplastin may also change the curve As these components possibly may be found following premature separation of the placenta the form of the TAT curves when the coagulation process of the blood has been activated and when

were normal HB was estimated to 75 % on the 7th day during the puerperium. The patient had no complaints when she was discharged one week after the delivery

Coagulation Analyses

Coagulation analysis for rapid determination of the fibrinogen content and of the fibrinolysis was performed by adding 0.2 ml thrombin ROCHE (20 NIH/ml) to a mixture of 0.2 ml undiluted plasma and 0.2 ml veronal buffer pH 7.4 If the fibrinogen content is sufficient and no anti thrombin is present a clot will be formed. This is incubated at 37 C for observation of fibrinolysis Normally this kind of clot is not dissolved within the first 24 hours. If clot formation failed or was insufficient the veronal buffer was replaced by 0.2 ml bovine fibrinogen 400 mg/100 ml, and the test was repeated.

The procedure for the drawing and preparation of blood samples was as previously described (Skjødt and Albrechtsen, 1965) The methods for the determination of hæmatocrit, platelet count recalcification time thromboplastin activation test (Astrup and Ollendorff 1961) the thromboplastin generation screening test (Hicks and Pitney 1957) the prothrombin—proconvertin (P P) factor V prothrombin and thrombin times the determination of fibrinogen measurement of fibrinolytic activity in plasma and in iso-electrically precipitated plasma (euglobulins) on standard fibrin plates and on heated fibrin plates and plasminogen determination have also been described previously (Skjødt and Albrechtsen 1965)

A detailed description is given only of the thromboplastin activation test according to Astrup and Ollendorff (1961) This analysis is an indication of the formation of plasma thromboplastin and of thrombin in plasma after recalcification Principally the technical procedure consists of repeated additions at intervals of one min in a period of 14 minutes of a small amount of the recalcified incubation mixture containing patient plasma to a series of test tubes with platelet poor human substrate plasma The coagulation times in the test tubes are recorded and the recalcification time in the incubation mixture is measured In a

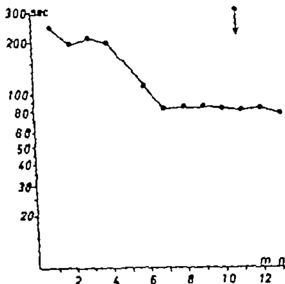


Fig. 3. TAT on normal, but platelet-poor human plasma (platelet count 68,000/mml) Plasma 25 ml + 0 25 ml 0083 molar $CaCl_2$ in ml veronal buffer pH 7.4.

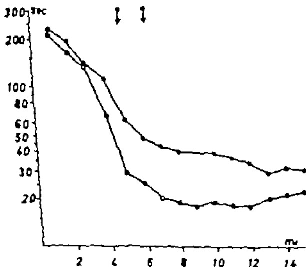


Fig. 4. ● ● TAT on normal, platelet-rich, human plasma (platelet count 398,000/mml) ○— —○ TAT on uterine serum 05 ml + normal platelet-rich, human plasma (platelet count 398,000/mml) 0.20 ml

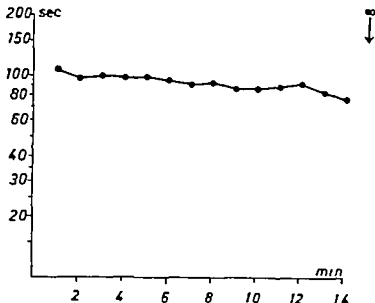


Fig. 2 TAT on uterine serum 0.25 ml+0.25 ml 0.0083 molar $CaCl_2$ in 2 ml veronal buffer pH 7.4

thrombocytopenia exists must be known Furthermore the effect of the addition of serum and tissue thromboplastin also must be determined. Some of these analyses have been published previ ously (Astrup and Ollendorff 1961 Astrup and Al brechtsen 1964 and Skjodt and Albrechtsen 1965)

1) It appears from earlier analyses that the blood discharged from the uterine cavity after normal delivery is unable to clot This is the end result of intrauterine coagulation with consumption of the fibrinogen of the blood (Greenberg, 1946 Bieniarz 1956 Schwenzer 1960 Skjodt and Albrecht sen 1965) so that blood expelled from the uterine cavity may be regarded as serum mixed with blood corpuscles squeezed out from an intrauterine clot.

Fig 2 reveals the result of the TAT performed upon uterine serum from a normal parturient woman As a result of failing formation of plasma thromboplastin and thrombin the clotting times are not progressively shortened and the recalcification time is indefinite. This is explained by the fact that it involves coagu lated blood where the platelets and the coagulation factors in the first and second phase have been consumed.

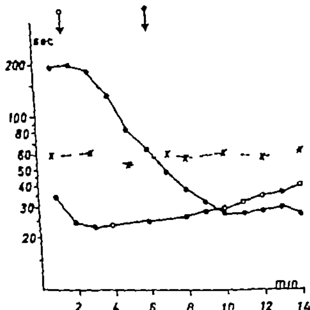


Fig. 6 ●——● TAT on normal, platelet-rich human plasma (platelet count 256,000/mml). ○——○ TAT on tissue thromboplastin ROCHE 0.05 ml+normal, platelet-rich plasma (platelet count 256,000/mml) 0.20 ml. x— —x control TAT on tissue thromboplastin ROCHE 0.05 ml+veronal buffer pH 7.4 .20 ml

effect of the serum upon the formation of plasma thromboplastin and thrombin manifests itself very strongly in spite of the reduced thromboplastin activation in the platelet-poor plasma.

5) Fig. 6 shows the TAT curves of normal human platelet-rich plasma (0.25 ml) and the same plasma (0 20 ml) with thromboplastin ROCHE (0.05 ml) added (of such a strength that 0 1 ml thromboplastin added to 0 1 ml normal, human plasma with subsequent recalcification results in a coagulation time of 14 seconds). At the same time fig. 6 shows a control curve with veronal buffer pH 7.4 (0 20 ml) with thromboplastin ROCHE (0.05 ml) added. It is evident that tissue thromboplastin *in vitro* causes a very early activation of the coagulation process in normal plasma. This rapid activation of the clotting process is not due solely to a tissue thromboplastin effect, but also to an acceleration of the

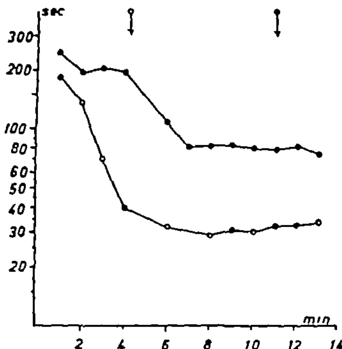


Fig. 5 ●——● TAT on normal but platelet-poor human plasma (platelet count 68,000/mml) ○——○ TAT on uterine serum 0.05 ml + normal, but platelet poor plasma (platelet count 68,000/mml) 0.20 ml.

2) Fig. 3 shows the progress of the TAT on thrombocytopenic human plasma (68 000 platelets/mml) The activation is clearly delayed and reduced and at the same time the recalcification time is prolonged.

3) Fig 4 shows the TAT curves for normal platelet-rich plasma (0 25 ml) and the same plasma (0.20 ml) with the addition of uterine serum (0 05 ml) The thromboplastin activation clearly is accelerated in the normal plasma as the clotting times are shortened. This acceleration starts four minutes after the addition of the uterine serum At the same time the recalcification time is shortened. This indicates that the serum contains a clot promoting component, described by Wessler (1955) as serum thrombotic accelerator (STA)

4) Fig 5 shows the TAT curve of thrombocytopenic human plasma (68 000 platelets/mml) (0 25 ml) and the same plasma (0 20 ml) with uterine serum (0 05 ml) added. The accelerating

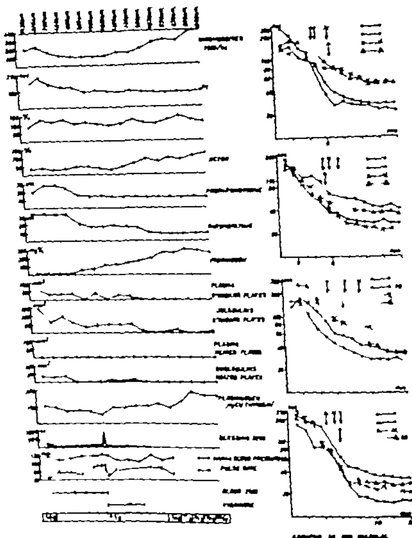


Fig. 8. The variations in the concentrations of the coagulation factors and the fibrinolytic components (platelet count, partial thromboplastin time (PTT), prothrombin-proconvertin (P-P), factor V, prothrombin and thrombin times, fibrinogen, fibrinolytic activity in plasma and in iso-electrically precipitated plasma (euglobulins) on standard fibrin plates and heat-treated plates, plasminogen) the amount of haemorrhage, the blood pressure and the pulse and the treatment instituted.

To the right of the figure the TAT curves are plotted. The numbering of the curves corresponds to the numeration of analyses given at the bottom of the figure. The corresponding recalcification times are indicated by arrows.

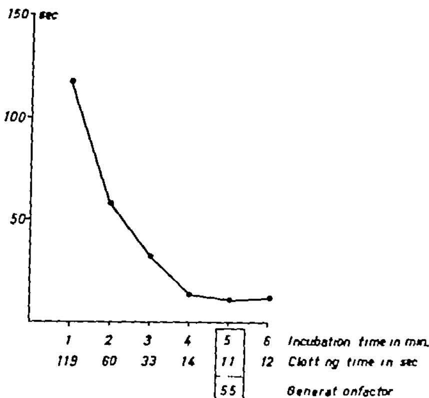


Fig 7 The thromboplastin generation screening test (*Hicks and Pitney*) Plotting of curve and calculation of the generation factor (GF) (see text)

thromboplastin activation in plasma produced by tissue thromboplastin as the measured clotting times are shorter than in the control curve

As with the thromboplastin activation test the thromboplastin generation screening test (Hicks and Pitney 1957) is an indication of the formation of plasma thromboplastin and thrombin after recalcification but with the difference that in the Hicks and Pitney test there is a surplus of thrombocyte factor The results of this test are expressed as a generation factor (GF) (Margulis *et al* 1965) instead of plotting them on a graph as previously GF is obtained by multiplying the shortest coagulation time (in seconds) with the corresponding incubation time (in minutes) (Fig 7) A reduced concentration of the clotting factors will result in a delayed and reduced thromboplastin generation manifesting itself as an increased GF

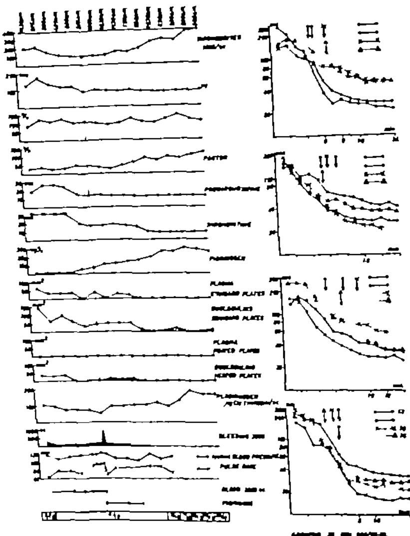


Fig 8 The variations in the concentrations of the coagulation factors and the fibrinolytic components (platelet count, partial thromboplastin time (PTT) prothrombin-proconvertin (P-P) factor V prothrombin and thrombin times, fibrinogen fibrinolytic activity in plasma and in iso-electrically precipitated plasma (euglobulins) on standard fibrin plates and heat-treated plates plasminogen) the amount of hemorrhage, the blood pressure and the pulse and the treatment instituted.

T the right of the figure the TAT curves are plotted. The numbering of the curves corresponds to the numeration of analyses given at the bottom of the figure. The corresponding recalcification times ar indicated by arrows.

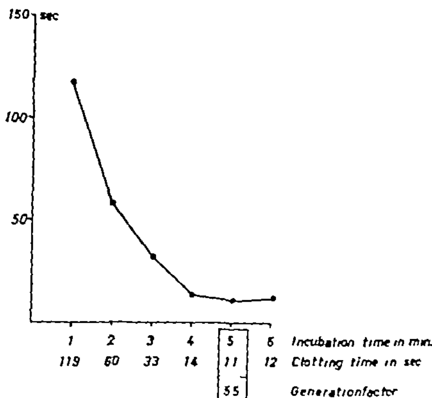


Fig 7 The thromboplastin generation screening test (*Hicks and Pitney*) Plotting of curve and calculation of the generation factor (GF) (see text)

thromboplastin activation in plasma produced by tissue thromboplastin as the measured clotting times are shorter than in the control curve

As with the thromboplastin activation test the thromboplastin generation screening test (Hicks and Pitney 1957) is an indication of the formation of plasma thromboplastin and thrombin after recalcification but with the difference that in the Hicks and Pitney test there is a surplus of thrombocyte factor The results of this test are expressed as a generation factor (GF) (Margulis *et al.* 1965) instead of plotting them on a graph as previously GF is obtained by multiplying the shortest coagulation time (in seconds) with the corresponding incubation time (in minutes) (Fig 7) A reduced concentration of the clotting factors will result in a delayed and reduced thromboplastin generation manifesting itself as an increased GF

Table I. The Thromboplastin Generation Screening Test (Hicks and Pitney) Expressed by GF in Normal Pregnant Parturient and Puerperal Women. At the Bottom of the Table GF is Given for Normal Non-pregnant Women between the Menstrual Periods.

			[illegible]	Range	Number
14 days before delivery	53-	±22.1	±5.5	24—104	9
– hour before delivery	52.4	±17.9	±5.7	28—75	9
Delivery	50.9	± 22	±3.5	33—72	1
1 hour after delivery	49.4	±15.9	±3.3	18—84	3
hours after delivery	50.0	±17.6	±5.0	30—84	7
3 hours after delivery	52.6	±21.5	±8.	22—84	7
24 hours after delivery	53.7	± 9.2	±7.3	30—90	7
week after delivery	52	±17.0	±5.4	32—84	9
4 weeks after delivery	54.4	± 5.1	±5.2	36—78	9
Normal non-pregnant women between the menstrual periods	55.4	±17.4	±3-	28—84	31

able but still prolonged. The fibrinogen concentration had gone up to 60 mg/100 ml and the fibrinolytic activity had decreased.

Shortly after delivery (9.20 a.m.) the patient had received a total of 2500 ml of blood. The coagulation conditions were further improved as the PTT was within the normal range (below 100 secs.) and the fibrinogen concentration continued to increase. During the infusion of 6 g of human fibrinogen shortly after delivery two venous blood samples were drawn. (10.00 and 10.30 a.m.) The fibrinogen concentration rose to 120 mg/100 ml and the plasminogen content increased. The remaining values were unchanged apart from a slightly increased fibrinolytic activity in the plasma.

At 11.30 a.m. haemorrhage had practically stopped. A total of 2 g of human fibrinogen had then been administered. The fibrinogen concentration had gone up to 140 mg/100 ml. Both the platelet count and the amount of factor V showed an increase.

During the first four hours after delivery (till 1.00 p.m.) the thrombin times were still prolonged in spite of the fact that the fibrinogen concentration rose above 100 mg/100 ml. This must indicate the presence of anti-thrombin. The addition of toluidine blue did not shorten the thrombin times.

Table I shows the GF of normal pregnant, parturient and puerperal women At the foot of Table I the GF for 31 non-pregnant women between the menstrual periods is given

Results

The results of the coagulation analyses of the patient are given in Fig 8 This also shows the extent of the haemorrhage the blood pressure and the pulse rate together with the amounts of blood and human fibrinogen administered.

In the first blood sample (Oct. 3 11 30 p.m) drawn before transfusion was commenced a low platelet count and a considerable prolongation of the partial thromboplastin time (PTT) were found The concentration of P–P expressing the total content of prothrombin and proconvertin was found to be reduced in relation to the values in normal parturient women (Skjødt and Albrechtsen 1965) Factor V was greatly reduced the prothrombin time was prolonged, but the thrombin times were indefinite The fibrinogen concentration was 15 mg/100 ml Moderately increased fibrinolytic activity was detected on standard fibrin plates indicating the presence of the plasminogen activator No free plasmin occurred as no activity was measured on heat treated plates In iso-electrically precipitated plasma (euglobulin fraction) a somewhat greater activity was measured on standard plates but a more moderate activity on heat treated plates The plasminogen content was clearly reduced.

While the first 1000 ml of blood was infused the coagulation conditions were analyzed thrice (Oct. 4 at 0 15, 2 00 and 4.05 a.m.) The platelet count continued to fall whilst the PTT remained prolonged. The concentrations of P–P were virtually unchanged but the prothrombin times were further prolonged. The thrombin times were indefinite and the fibrinogen concentrations remained very low The fibrinolytic conditions were unchanged.

About one hour before the delivery (8 00 a.m) a total of 1700 ml of blood had been administered, and at this time signs of improvement in the coagulation status were found. The prothrombin time was shortened and the thrombin time was measur

the recalcification times were prolonged again, while the last curves (nos. 14–16) were within the normal range.

The results of the thromboplastin generation screening test (Hicks and Pitney 1957) expressed by GF are given in Table II. In the first seven samples the GF was considerably higher than the average values at the corresponding times in normal parturient women (Table I) and much higher than GF in the patient after the coagulation status had returned to normal. Samples no 2 and no. 6 are exceptions as they were considerably lower than the GF in the control group (Table I) The high GF values indicate a reduced thromboplastin generation and correspond with the results of the thromboplastin activation test. The pronounced shortenings in GF were co-incident with the characteristic changes in the course of the TAT curves and the analogous reductions in the recalcification times.

The results of the hæmatocrit determinations are given in Table III In the early stages the values were low and did not return to normal until two weeks after delivery

Discussion

It is Schneider s opinion (1959) that the earlier in the preg nancy the separation of the placenta occurs the more likely is a serious defibrination and hæmorrhagic diathesis. This may be due to the fact that the earlier the separation takes place the more unfavourable are the circumstances of vaginal delivery The above mentioned case occurred as early as in the 26th week.

The patient was admitted 3½ hours after the symptoms began. Thus it was possible to make analyses at an early stage in the development of the disease. However no coagulation studies were performed at the time of admission, but the spontaneous coagula tion time was normal and this gives a gross indication of sufficient content of fibrinogen in the blood. Two hours later the fibrinogen concentration was 15 mg/100 ml. This points towards a rapid development of defibrination. It has not yet been explained how the coagulation defect originates. Schneider (1959) thinks that tissue thromboplastin from placenta and decidua passes into the maternal circulation and causes transformation of the fibrin-

Table II. *The Thromboplastin Generation Screening Test (Hicks and Pitney) Expressed by GF in the Patient at Various Times.*

Oct. 3	11 30 p.m.	1	78.0	Oct. 4	11 30 a.m.	9	30.0
Oct. 4	0 15 a.m.	2	45.0	Oct. 4	1 00 p.m.	10	33.0
Oct. 4	2 00 a.m.	3	104.0	Oct. 4	5 00 p.m.	11	36.0
Oct. 4	4 05 a.m.	4	72.0	Oct. 5	10.30 a.m.	12	35.0
Oct. 4	8.00 a.m.	5	79.0	Oct. 7	8 30 a.m.	13	35.0
Oct. 4	9 20 a.m.	6	45.0	Oct. 9	8 30 a.m.	14	40.0
Oct. 4	10.00 a.m.	7	72.0	Oct. 16	9 00 a.m.	15	[illegible]8.0
Oct. 4	10 30 a.m.	8	55.0	Oct. 30	9 00 a.m.	16	35.0

Table III. *The Serial Hæmatocrit Values in Per Cent*

Oct. 3	11 30 p.m.	1	25	Oct. 4	11 30 a.m.	9	32
Oct. 4	0 15 a.m.	2	25	Oct. 4	1 00 p.m.	10	33
Oct. 4	2.00 a.m.	3	24	Oct. 4	5 00 p.m.	11	32
Oct. 4	4 05 a.m.	4	25	Oct. 5	10 30 a.m.	12	34
Oct. 4	8.00 a.m.	5	26	Oct. 7	8 30 a.m.	13	34
Oct. 4	9.20 a.m.	6	28	Oct. 9	8 30 a.m.	14	36
Oct. 4	10 00 a.m.	7	29	Oct. 16	9.00 a.m.	15	40
Oct. 4	10 30 a.m.	8	30	Oct. 30	9.00 a.m.	16	41

Nearly eight hours after delivery (5 00 p.m.) the fibrinogen concentration was 195 mg/100 ml and the remaining values were normal.

The results of the TAT are also given in Fig 8

The first two curves (nos. 1 and 2) had a normal course and at the same time the recalcification times were short (270 and 330 secs) It must be noted that the reading of the recalcification times was *somewhat uncertain as* the clot formation had the character of gritty precipitation due to the low fibrinogen values.

Apparently these TAT curves express normal formation of plasma thromboplastin and thrombin The following curves (3 4 and 5) were clearly flattened and the corresponding recalcification times prolonged as an indication of a reduced formation of the plasma thromboplastin and thrombin

The next curves (6 and 7) in Fig 8 showed renewed improvement towards normality and the recalcification times were shortened again The curves nos 8–13 were slightly flattened and

the concurrent severe coagulation defects. An activation of the clotting process as well as an increased fibrinolytic activity cause reduced content of several of the coagulation factors involved in the formation of plasma thromboplastin and thrombin. Therefore it would be expected that the curve would be flattened and the recalcification time prolonged (*cf* Figs. 2 and 3) Thus it may be reasonable to assume that the normal progress of the thromboplastin activation in the first analysis was due to the presence of clot-promoting components in the blood. This may well result from the passage of tissue thromboplastin and serum from the uterine cavity into the maternal circulation.

The acceleration of the thromboplastin activation described could be found again 45 minutes later (curve 2) and occurred again at the time of delivery (curves 6 and 7) In the intervening period signs of reduced formation of plasma thromboplastin and thrombin were found. This may be explained by the low platelet count and a further fall in the content of the factors taking part in the first phase of the coagulation process. Tissue thromboplastin and serum may still have been present in this period without being disclosed by the present technique used for the TAT This may have been due to the fact that the concentration of the coagulation factors was so severely reduced that existing clot promoting factors did not have sufficient substrate on which to produce an effect.

It appears from Fig. 8 and Table II that around and especially just after delivery there was increased formation of plasma thromboplastin and thrombin. This may be explained by an increase in the concentrations of the coagulation factors, so that the presence of clot promoting substances could now be registered through the effect on these It is seen from the TAT curves that it was not a question of normalization of the thromboplastin activation as already one hour and a half after the delivery the curves were flattened again.

The intermittent occurrence of increased coagulation activity may probably also be connected with the strong uterine tone before the rupture of the membranes and the intense contractions during oxytocin infusion in the last phase of the delivery These conditions may have favoured the passing of clot-promoting

ogen of the blood into fibrin In severe cases this may cause shock dyspnœa and cyanosis if the fibrin is precipitated in the pulmonary vessels. On the other hand Stouffer and Ashworth (1958) and Nilsen (1963) believe that the hypo- or afibrinogenemia and the fall in various other coagulation factors are due to the fact that the factors are consumed during the formation of the retroplacental clot. Finally several authors and among them Phillips *et al* (1962) are of the opinion that the coagulation defect is caused essentially by a greatly increased fibrinolytic activity

The results of the analyses of the first four blood samples in the above mentioned case revealed a gross coagulation defect P-P % was clearly reduced the factor V content was markedly reduced and the fibrinogen concentration extremely low coincident with an increase in the fibrinolytic activity Corresponding with these changes PTT was found to be considerably prolonged. This test gives an expression of all the components in the three phases of the coagulation process with the exception of factor VII (proconvertin) Thus the PTT is suitable as a screening test in acute situations creating a suspicion of a coagulation abnormality

The defects demonstrated in the clotting mechanism may be due to the increased fibrinolytic activity alone but they may also be caused by an activation of the coagulation process intravascular or intrauterine The existing anti thrombin activity does not permit any certain conclusions as to the causal relationships as anti thrombin may generate as a result of coagulation (Klein and Seegers 1950) and due to a fibrinogenolytic decomposition caused by plasmin (Bang, Fletcher Alkjærsig, and Sherry 1962)

Only the low *falling platelet count points towards an activation of the coagulation process.* Thrombocytopenia is caused by a coagulation process while the platelet count is unreduced by increased fibrinolysis (Koller 1961)

The results of the thromboplastin activation test (TAT) point towards an activation of the coagulation process. The TAT in the first analysis (Fig 8 curve 1) apparently indicated a normal formation of plasma thromboplastin and thrombin simultaneous with a short recalcification time This is remarkable considering

The progress in the above mentioned case may be due to passage of serum from the retroplacental haematoma to the maternal circulation and to intravascular coagulation caused by tissue thromboplastin with secondary liberation of serum from intra vascularly precipitated fibrin.

The clinical course gives no information which helps to elucidate the problem. At no time was there respiratory embarrass ment indicating obstetric shock (Schneider 1959) but this does not exclude a slight intravascular activation of the coagula tion process.

The patient s massive retroplacental clot formation was undoubtedly of great importance in the development of the coagula tion defect. The active transfusion treatment is probably the reason why the great concealed loss of blood did not cause shock, but it might also be reasonable to assume that the passage of serum into the maternal circulation contributed to the maintenance of the circulating blood volume This point of view is supported by the relatively low haematocrit values despite the repla cement of the measured loss of blood.

The large massive retroplacental clot and the results of the analyses indicate that the coagulation defect is largely due to a consumption of the coagulation factors by the retroplacental coagulation Moreover STA was demonstrated in the blood. This may be a result of the passage of serum into the maternal circula tion, but also of serum yielded from intravascularly precipitated fibrin The increased fibrinolytic activity may be regarded as secondary released by the coagulation activation as part of the haemostatic balance (Astrup 1958) as no shock occurred as a factor provoking fibrinolysis. Intravascular coagulation may have taken place to a certain extent, because intrauterine precipitation of fibrin is unlikely to cause activation of fibrinolysis in the circulating blood.

The TAT and the remaining analyses of coagulation and fibrinolysis have been performed according to the above mentioned principles in another 20 patients with premature separa tion of the placenta and decreasing fibrinogen concentration. Eight of these patients had large retroplacental clot formation and a fibrinogen concentration of $\geq$ 150 mg/100 ml. The results

substances from the retroplacental haematoma into the maternal circulation.

The results of the Hicks and Pitney test seem to confirm this intermittent occurrence of increased coagulation activity in the blood (Table II) Thus the GF in blood samples 2 and 6 were very low (45) It is reasonable to assume that this was due to clot promoting components in the blood. However there was not complete accordance between the increased coagulation activity shown by the TAT and the Hicks and Pitney test, as GF in the first analysis was increased. This may be due to the fact that the Hicks and Pitney test is less sensitive than the TAT

Thus the results of the TAT and the Hicks and Pitney test as well as the results of the remaining coagulation analyses indi cate the presence of clot promoting components in the blood. However the results of the analyses cannot establish whether these originated from the passage of tissue thromboplastin from plancenta and decidua or whether they were caused by passing of serum from the retroplacental haematoma to the maternal circulation

The TAT tests performed with the addition of uterine serum (from normal parturient women) and tissue thromboplastin (ROCHE) to normal human plasma should offer an opportunity to differentiate between thromboplastin and serum infusion Uter ine serum causes acceleration of thromboplastin activation in normal plasma after four minutes (Figs. 4 and 5) while the clot promoting effect of the tissue thromboplastin manifests itself strongly during the earliest phase of the formation of plasma thromboplastin (Fig 6) The changes in the courses of the TAT curves caused by tissue thromboplastin could not be reproduced in animal experiments It has not been possible to demonstrate the characteristic early commencing acceleration shortly after the i.v injection of large doses of tissue thromboplastin In such experiments gross intravascular coagulation occurred with total consumption of the fibrinogen of the blood. That no tissue throm boplastin could be demonstrated is probably due to the fact that this was removed at once after the intravascular coagulation pos sibly in the reticulo-endothelial system (Albrechtsen and Brakman personal communication)

The progress in the above mentioned case may be due to passage of serum from the retroplacental haematoma to the maternal circulation and to intravascular coagulation caused by tissue thromboplastin with secondary liberation of serum from intravascularly precipitated fibrin.

The clinical course gives no information which helps to elucidate the problem. At no time was there respiratory embarrassment indicating obstetric shock (Schneider 1959) but this does not exclude a slight intravascular activation of the coagulation process

The patient's massive retroplacental clot formation was undoubtedly of great importance in the development of the coagulation defect. The active transfusion treatment is probably the reason why the great concealed loss of blood did not cause shock, but it might also be reasonable to assume that the passage of serum into the maternal circulation contributed to the maintenance of the circulating blood volume. This point of view is supported by the relatively low haematocrit values despite the replacement of the measured loss of blood.

The large massive retroplacental clot and the results of the analyses indicate that the coagulation defect is largely due to a consumption of the coagulation factors by the retroplacental coagulation. Moreover STA was demonstrated in the blood. This may be a result of the passage of serum into the maternal circulation but also of serum yielded from intravascularly precipitated fibrin. The increased fibrinolytic activity may be regarded as secondary released by the coagulation activation as part of the haemostatic balance (Astrup 1958) as no shock occurred as a factor provoking fibrinolysis. Intravascular coagulation may have taken place to a certain extent, because intrauterine precipitation of fibrin is unlikely to cause activation of fibrinolysis in the circulating blood.

The TAT and the remaining analyses of coagulation and fibrinolysis have been performed according to the above mentioned principles in another 20 patients with premature separation of the placenta and decreasing fibrinogen concentration. Eight of these patients had large retroplacental clot formation and a fibrinogen concentration of $\leqq$ 150 mg/100 ml. The results

of these TAT analyses indicate the presence of STA in the blood. Thus the conclusions drawn on the basis of the case in question seem to be confirmed (Skjodt in preparation)

The hypofibrinogenaemia was diagnosed ten hours before the delivery At this time no infusion of human fibrinogen was administered due to the risk of intravascular precipitation of added fibrinogen (Albrechtsen and Skjodt 1964) Nor was treatment with antifibrinolytic substances indicated as the fibrinolytic activity was only moderately increased. Furthermore fibrinolytic activity within certain limits must be regarded as a defensive mechanism restraining possible results of the intra vascular coagulation by removing intravascularly precipitated fibrin

After the delivery a total of 12 g of human fibrinogen was administered During this the fibrinogen concentration rose to 140 mg/100 ml which is less than would be expected for the amount infused. There is no reasonable explanation for the relatively moderate increase in the concentration. Even though the clot-promoting STA was present in the blood at the beginning of the fibrinogen infusion it caused hardly any consumption of fibrinogen by intravascular activation of the coagulation process, as the patient was not shocked. Thus (Wessler 1955) proved that the STA only accelerates the coagulation process in parts of the circulatory system where stasis prevails The fibrinolytic activity was not so great that any important fibrinogenolysis took place A certain amount of fibrinogen is probably used for the intrauterine coagulation as part of the normal hæmostatic process after delivery Finally it is possible that some of the fibrinogen in the preparation used had been denatured.

It must be emphasized that the results of the TAT in the present circumstances can only be judged when the remaining analyses of coagulation and fibrinolysis are performed simultaneously *Failing* these the *results may* be directly misleading, since an eventual activation of the coagulation process in a patient with a severe coagulation disturbance may indicate a normal forma tion of plasma thromboplastin and thrombin Besides the TAT cannot always reveal the presence of the STA As mentioned above there must be a sufficient amount of activatable coagula

tion factors, and this can only be revealed by a modification of the thromboplastin activation test. Such investigations are already planned.

SUMMARY

An account is given of a case of severe premature separation of the placenta with large retroplacental clotformation and with hypofibrinogenaemia in the peripheral blood. Several analyses of coagulation and fibrinolysis were performed. These analyses disclosed the hypofibrinogenemia, low concentrations of the remaining coagulation factors and activation of the fibrinolytic enzyme system of the blood.

Among the methods of analysis used the thromboplastin activation test according to Astrup and Ollendorff (1961) was of special value. Compared with other coagulation analyses the results of this analysis indicated the presence of a clot-promoting component, probably of the same character as the serum thrombotic accelerator (STA) described by Wessler (1955)

The presence of the serum thrombotic accelerator in the blood indicates an activation of the coagulation process. It is possible that the STA passed into maternal circulation with the serum squeezed out of the retroplacental clot, which seems to be a fundamental cause of the coagulation defect. The serum thrombotic accelerator may also have originated from serum yielded to the circulating blood from an intravascular precipitation of fibrin due to tissue thromboplastin from placenta and decidua.

The coagulation defect was detected ten hours before spontaneous delivery The patient was treated with blood transfusion before delivery and with human fibrinogen after delivery

REFERENCES

Albrechtsen O K and Skjødt P Danish Med Bull 9, 179, 1962
Albrechtsen O K and Skjødt P Acta obst. et gynec. scandinav 43 129 1964
Albrechtsen O K., and Brakman P personal communication
Astrup T Thromb. Diathes. haemorrh., 2 347 1958

of these TAT analyses indicate the presence of STA in the blood. Thus the conclusions drawn on the basis of the case in question seem to be confirmed (S k j ø d t in preparation)

The hypofibrinogenaemia was diagnosed ten hours before the delivery At this time no infusion of human fibrinogen was administered due to the risk of intravascular precipitation of added fibrinogen (A l b r e c h t s e n and S k j ø d t 1964) Nor was treatment with antifibrinolytic substances indicated as the fibrinolytic activity was only moderately increased. Furthermore fibrinolytic activity within certain limits must be regarded as a defensive mechanism, restraining possible results of the intra vascular coagulation by removing intravascularly precipitated fibrin

After the delivery a total of 12 g of human fibrinogen was administered. During this the fibrinogen concentration rose to 140 mg/100 ml which is less than would be expected for the amount infused. There is no reasonable explanation for the relatively moderate increase in the concentration Even though the clot promoting STA was present in the blood at the beginning of the fibrinogen infusion it caused hardly any consumption of fibrinogen by intravascular activation of the coagulation process as the patient was not shocked. Thus (W e s s l e r 1955) proved that the STA only accelerates the coagulation process in parts of the circulatory system where stasis prevails. The fibrinolytic activity was not so great that any important fibrinogenolysis took place A certain amount of fibrinogen is probably used for the intrauterine coagulation as part of the normal hæmostatic process after delivery Finally it is possible that some of the fibrinogen in the preparation used had been denatured

It must be emphasized that the results of the TAT in the present circumstances can only be judged when the remaining analyses of coagulation and fibrinolysis are performed simultaneously Failing these the results may be directly misleading since an eventual activation of the coagulation process in a patient with a severe coagulation disturbance may indicate a normal forma tion of plasma thromboplastin and thrombin Besides the TAT cannot always reveal the presence of the STA As mentioned above there must be a sufficient amount of activatable coagula

Skjødt Preben, Acta obst. et gynec. scandinav. 46, [illegible] 1967
From the State Maternity Hospital Aarhus (Professor M. Lagerlev) and the Blood Group Laboratory (F. Kissmeyer-Nielsen M. D.) the Municipal Hospital Aarhus, Denmark

CLOTPROMOTING COMPONENTS IN CIRCULATING BLOOD IN A CASE OF ABRUPTIO PLACENTÆ WITH AFIBRINOGENEMIA

BY

PREBEN SKJØDT

Introduction

Several authors regard the passing of tissue thromboplastin from placenta and decidua into the maternal circulation as the cause of the hæmorrhagic diathesis which may occur in patients with premature separation of the placenta (Schneider 1959 Mc Kay 1965). This kind of process will lead to consumption of several coagulation factors, including the fibrinogen of the blood, with resulting deficient coagulability. When fibrin is formed by intravascular coagulation ultimate retraction of the clot yields serum to the circulation blood (Astrup and Albrechtsen, 1964).

An alternative view is that the most important cause of the coagulation defect in patients with premature separation of placenta is consumption of the coagulation factors as retroplacental coagulation proceeds. The retroplacental clot also will retract and liberate serum. The increased uterine tone may cause passage of the serum into the peripheral blood (Nilsen, 1963 Skjødt, 1967).

The presence of serum in the circulating blood is of special interest, because it shows that an activation of the coagulation process has taken place—either intravascularly or retroplacentally. Serum contains Wessler's serum thrombotic accelerator

Astrup T and *Ollendorff P* Scand. J Clin. & Lab Invest 13 377 1961
Astrup T and *Albrechtsen O K.* Fed Proc. 23 354 1964
Bang, N U Fletcher A. P and *Sherry S* J Clin Invest. 41 935 1962
Bienlar J Zentralbl. Gynäk. 78 1369, 1956
Greenberg E. M Am. J Obst. & Gynec 52 746 1946
Hicks N D and *Pitney W R.* Brit. J Hematology 3 228 1957
Klein P D and *Seegers W H* Blood 5 742 1950
Koller F Therapie Der Hämorrhagischen Diathesen. J Frey und J Jürgens Stuttgart. Schattauer 1961 p 3.
Margulis R. R. Ambrus J L. Mink I B. and *Stryker J C.* Am. J Obst. & Gynec. 93 161 1965
Nilsen P A. Acta obst. et gynec scandinav 42 1963 Suppl. 2
Phillips L. L. Skrodelis W and *Taylor Jr H C* Am. J Obst. & Gynec 84 1447 1962
Schneider C. L. Ann. N Y Acad. Sci 75 634 1959
Schwenzer A. W Arch. Gynäk. 195 114 1960
Skjodt P and *Albrechtsen O K.* Acta obst. et gynec. scandinav 44 416 1965
Skjodt P In prep
Stouffer J G and *Ashworth C T* Am J Obst. & Gynec 75 407 1958
Wessler S J Clin. Invest. 34 647 1955

Received on May 15th 1966

Skjodt, Preben, Acta obst. et gynec. scandinav. 46, 41, 1967
From the State Maternity Hospital Aarhus (Professor M. Ingerslev) and the Blood Group Laboratory (F. Kissmeyer-Nielsen, M. D.) the Municipal Hospital Aarhus, Denmark

CLOTPROMOTING COMPONENTS IN CIRCULATING BLOOD IN A CASE OF ABRUPTIO PLACENTÆ WITH AFIBRINOGENEMIA

BY

PREBEN SKJODT

Introduction

Several authors regard the passing of tissue thromboplastin from placenta and decidua into the maternal circulation as the cause of the hæmorrhagic diathesis which may occur in patients with premature separation of the placenta (Schneider 1959, Mc Kay 1965). This kind of process will lead to consumption of several coagulation factors, including the fibrinogen of the blood, with resulting deficient coagulability. When fibrin is formed by intravascular coagulation ultimate retraction of the clot yields serum to the circulation blood (Astrup and Albrechtsen, 1964).

An alternative view is that the most important cause of the coagulation defect in patients with premature separation of placenta is consumption of the coagulation factors as retroplacental coagulation proceeds. The retroplacental clot also will retract and liberate serum. The increased uterine tone may cause passage of the serum into the peripheral blood (Nilsen, 1963, Skjodt, 1967).

The presence of serum in the circulating blood is of special interest because it shows that an activation of the coagulation process has taken place—either intravascularly or retroplacentally. Serum contains Wesslers serum thrombotic accelerator

Astrup T and *Ollendorff P* Scand. J Clin. & Lab Invest. *13* 377 1961
Astrup T and *Albrechtsen O K.*, Fed. Proc. 23 354 1964
Bang N U *Fletcher A. P* and *Sherry S* J Clin. Invest *41* 935. 1962
Biendar J Zentralbl. Gynäk. 78 1369 1956
Greenberg, E. M Am. J Obst. & Gynec. 52 746 1946
Hicks N D and *Pitney W R* Brit. J Hematology *3* 228 1957
Klein P D and *Seegers W H* Blood 5 742 1950
Koller F Therapie Der Hämorrhagischen Diathesen. J Frey und J Jürgens. Stuttgart. Schattauer 1961 p 3
Margulis R R. *Ambrus J L.* *Mink I B* and *Stryker J C.* Am. J Obst. & Gynec. 93 161 1965
Nilsen P A. Acta obst. et gynec scandinav *42* 1963, Suppl. 2
Phillips L. L. *Skrodelis W* and *Taylor Jr H C.* Am. J Obst. & Gynec. *84* 1447 1962
Schneider C. L. Ann. N Y Acad. Sci. 75 634 1959
Schwenzer A. W Arch. Gynäk *195* 114 1960
Skjødt P and *Albrechtsen O K.* Acta obst. et gynec. scandinav *44* 416 1965
Skjødt P In prep
Stouffer J G and *Ashworth C. T* Am. J Obst. & Gynec. 75 407 1958
Wessler S J Clin. Invest. *34* 647 1955

Received on May 15th 1966

rate 70 Weak contractions and good foetal sounds. The patient now received allypropymal 100 mg and menadion sodium bisulfit 1 mg×4

On May 22 at 50 m. the patient had been resting well for the preceding four hours. Blood pressure 120/80, pulse rate 76 Contractions at intervals of 4–5 min. N increased uterine tension and good foetal heart sounds. Only moderate aginal bleeding.

At 4 5 a.m. the patient was troubled by rapidly progressive uterine contractions. The uterus was now tense and no foetal heart sounds could be heard. Oxygen was administered by nasal catheter Slight vaginal bleeding continued. Blood pressure 110/70.

At 5.45 m. vaginal examination was performed. The cervix admitted one finger Rupture of the membranes yielded copious clear amniotic fluid. Foetal heart sounds still could not be heard. Infusion of 5 % of glucose was started.

At 7 30 m. the uterine tension increased again after transient relief evoked by the amniotomy

At 8.00 m. the patient was in pain and was rather restless. 75 mg of pethidine was administered with good effect.

At 8 30 m. the blood pressure was 105/80 and the pulse rate 70 of good volume. Rapid analysis (see methods) revealed complete lack of f brinogen, but no signs of increased fibrinolysis.

At 9 50 a m. blood transfusion (no. 1) was started

At .00 a.m. there was increased uterine activity with pain and slight aginal bleeding There was no dyspnoea or cyanosis. Blood pressure was 05/65, pulse rate 75 Vaginal examination showed that the cervix still only admitted one finger 4 mg of morphine was administered.

At 55 m. the patient was calmer The uterus felt tense and there were contractions at intervals of three minutes. The blood pressure was 10/90 the pulse rate 70. Another transfusion (no.) was given.

At 0.35 p m. infusion was started of oxytocin 1 u./ 000 ml 5 % glucose. The contractions increased in intensity rapidly and the patient was in increasing pain 5 minutes later there was profuse gush of fresh blood from the vagina and the patient became very pale with transient loss of consciousness. There was neither cyanosis nor respiratory embarrassment. The blood pressure dropped to 90 mm systolic. The infusion of oxytocin was stopped, and the patient was placed in Trendelenburg position, while the next blood transfusion (no 3) was started Her condition improved very quickly the blood pressure increased to 20/90 and the pulse was of good volume There was no haematuria, nor cutaneous or mucosal haemorrhages.

At 00 p m. the infusion of oxytocin was resumed.

At 30 p m. the contractions were increasing with intervals of two minutes. The blood pressure was 5/8 The loss of non-coagulated blood from vagina increased

At 00 p.m. the patient was in great pain. The blood pressure was 20/80 5 mg of pethedine was administered intramuscularly and shortly after the patient began to bear down.

(STA) (1955) which possesses clot promoting potential. The thromboplastin activation test (Astrup and Ollendorff 1961) makes it possible to demonstrate STA in the blood. In a case of premature separation of placenta with hypofibrinogenemia the results of this test together with the remaining analytic results indicated the presence of STA in the patient's peripheral blood (Skjodt, 1967) In that report only determination of the thromboplastin activation in the patient's plasma was performed (two-stage TAT) and no analysis was made of the eventual clot promoting effect of the patient's plasma upon normal human plasma (three-stage TAT) The latter analysis reveals the presence of a serum factor in the blood more readily

An account is given here of a case of premature separation of placenta with severe hypofibrinogenemia An attempt has been made to apply the above mentioned approach using conventional analyses of coagulation and fibrinolysis supplemented by the thromboplastin activation test both two-stage and three-stage

Case Report

J no 385/65–66 24 year-old gravida I para O No hereditary tendencies towards hæmorrhagic diathesis. Previously healthy apart from transient irregular menstrual periods three years before the present admission. Last menstrual period Sept. 30 and expected date of confinement July 7

On *February 1st–3rd* she had slight painless vaginal bleeding, and stayed home in bed for ten days Apart from this there were no complications during the pregnancy and in particular no proteinuria, hypertension or œdema.

On *May 21* at 5 30 p.m. she was admitted to hospital with moderate fresh vaginal bleeding of one hour's duration. On admission she had some pain in the umbilical region. Her general condition was good and she had no obvious anæmia. Her uterus was diffusely tender and slightly tense. The fœtus presented by the head, fœtal heart sounds were normal 120/min. Blood pressure 130/100 pulse volume good.

At 8 15 p.m. there were irregular uterine contractions. The uterine tension had decreased. There was slight oozing from the vagina. The fœtal heart sounds were normal. By catheterization 100 ml clear urine free from protein was obtained.

At 8.45 p.m. the patient was comfortable warm. Blood pressure and pulse rate were normal. There was minimal increase in uterine tone with weak irregular contractions. Slight vaginal bleeding continued.

At 9.30 p.m. her condition was unchanged. Blood pressure 110/70 pulse

However increased thromboplastic activity in plasma is more readily demonstrated by the three-stage thromboplastin activation test. In principle this modification of the test aims at measuring any clot-promoting components that might occur in the patient's plasma by means of its coagulation accelerating effect upon normal human, platelet-rich plasma.

The incubation mixture here consists of 2.0 ml veronal buffer pH 7.4+0.20 ml normal human, platelet-rich plasma+0.05 ml platelet-containing patient plasma+0.25 ml 0.025 molar calcium chloride.

In a previous paper (Skjødt, 1967) it was shown that both human serum and tissue thromboplastin (ROCHE) acted as coagulation accelerators as judged by their effect upon thromboplastin activation in normal human plasma. While the coagulation accelerating effect of the serum only began after four minutes incubation, the coagulation accelerating effect of the tissue thromboplastin was evident after one minute.

The thromboplastin generation screening test (Hicks and Pitney 1957) was performed as previously described (Skjødt, 1967) and the results were expressed as the generation factor (GF). This test assesses the formation of plasma thromboplastin and thrombin but since surplus thrombocyte factors are present the results obtained give only an indication of the total plasma coagulation factors.

The serum from the patient was obtained from venous blood collected in ordinary glass tubes. After spontaneous coagulation had taken place the glass tubes were incubated in a water-bath at 37 C for two hours followed by centrifugation at 3500 rpm for 30 minutes. The serum was removed by pipette and used for the two-stage TAT and the three-stage TAT on the patient's own peripheral plasma four weeks after delivery.

Results

The results of the coagulation analyses are shown in fig. 1. The blood pressure pulse rate amount of haemorrhage and treatment re also detailed. In the first two analyses (on May 22 at 8.30 and 9.30 a.m.) both performed before the blood transfusion was started, the results were practically identical. They disclosed a

At 3.25 p.m. an episiotomy was made and ten minutes later a still-born boy was delivered. The weight was 2680 g and the length 51 cm. When the shoulders were delivered 0.2 mg of methergin was administered intravenously. Delivery of the placenta occurred immediately and was associated with heavy bleeding. 900 g compact clots and 1300 ml non-coagulated blood was collected. The placenta had a 10×10 cm deep impression at the periphery but no infarcts were seen. The uterus contracted well after increased infusion of oxytocin and the bleeding decreased quickly. There was no exceptional bleeding from the episiotomy. Before delivery the bleeding was estimated to about 600 ml and the total loss of blood before, during and after delivery was estimated at 3000 ml. At the end of the delivery the blood pressure was 120/80.

Later three more bottles of blood (nos. 4,5 and 6) were infused. There was no bleeding and the blood pressure was constantly about 120/80 and the pulse rate 76. The puerperium was without complications. On May 24, the Hb was 76 % and the blood pressure about 120/70. There was no proteinuria and the urinary output was satisfactory about 1000 ml in 24 hours, the specific gravity was from 1011–1016. The temperature was normal, the patient was discharged seven days after delivery.

Methods

The drawing of the blood samples and the preparation of the venous and uterine blood was performed as described previously (Skjodt and Albrechtsen 1965) (Skjodt, 1967). The platelet count, the partial thromboplastin time (PTT), prothrombin-proconvertin (P P), fibrinolytic activity in plasma and in the euglobulin fraction of the plasma on standard fibrin plates and on heat treated plates, plasminogen and hæmatocrit were also carried out as in previous investigations.

The rapid analysis for determination of the fibrinogen content and the fibrinolytic activity was performed as described previously by adding thrombin to plasma (Skjodt, 1967).

The thromboplastin activation test (Astrup and Ollendorff 1961) was performed in two-stages described previously (Skjodt and Albrechtsen 1965, Skjodt, 1967). This test indicates the formation of plasma thromboplastin and thrombin in the plasma after recalcification. The results are plotted on a graph, with the incubation times in minutes as the abscissa and the logarithm of the coagulation times as the ordinate. The resulting curve is characterized by the following values: t 1, T max, t max, t 14 and the recalcification time. Compared with the remaining coagulation analyses this test may help to elucidate whether increased thromboplastic activity is found in the plasma.

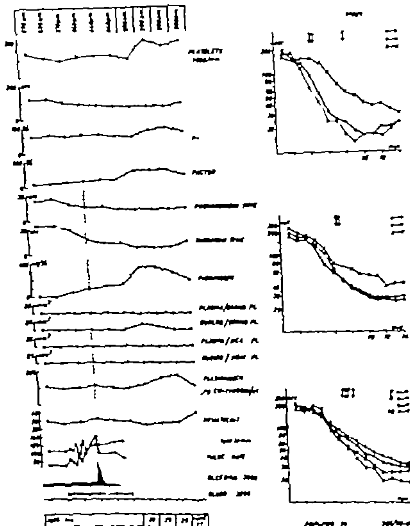


Fig. The variations in the concentration of the coagulation factors (platelet count, partial thromboplastin time (PTT) prothrombin-proconvertin (P-P) factor V prothrombin and thrombin times and fibrinogen concentration) in the content of fibrinolytic components (fibrinolytic activity in plasma and in no-electrically precipitated plasma (euglobulins) measured upon standard fibrin plates and on heated plates and the plasminogen content) and in the haematocrit.

T the right of the figure the results of the two-stage TAT are given. The numbering of the curves corresponds with the numeration of the analyses at the bottom of the figure. The corresponding recalcification times are indicated by arrows.

pronounced coagulation defect. Thus afibrinogenemia was found together with low platelet count and a prolonged partial thromboplastin time (PTT) of 117 and 124 secs. The prothrombin-proconvertin value (P P) was decreased as compared with the values in normal parturient women The content of factor V was considerably reduced The prothrombin times were markedly prolonged and the thrombin times were indefinite. No fibrinolytic activity was measured in plasma or in iso-electrically precipitated plasma (the euglobulin fraction) on standard fibrin plates or on heat treated fibrin plates. However the plasminogen content was somewhat reduced as compared with normal parturient women (Skjodt and Albrechtsen 1965)

The next two analyses (at 2 30 and 3.40 p.m.) showed signs of improvement in the coagulation status During this period a total amount of 2000 ml blood was administered. The fibrinogen concentration rose to 58 mg/100 ml and 94 mg/100 ml respectively At the same time the platelet count after a transient fall began to increase The PTT was now within the normal range, i e below 100 secs The P P values were unchanged but the factor V concentration increased. The prothrombin time had shortened and the thrombin times could be measured but were still prolonged. There were still no signs of increased fibrinolysis determined by the fibrin plate method and the plasminogen values were unchanged.

The following two analyses (4 40 and 6.40 p.m.) showed further signs of improvement. After delivery another 1000 ml blood had been infused. Yet the coagulation status was not quite normal as the fibrinogen concentration (at 6.40 p.m.) was only 140 mg/100 ml. Furthermore the platelet count was still low (120 000/mml) the factor V concentration was only 41 % The thrombin time was still slightly prolonged (13 secs) in spite of a sufficient content of fibrinogen presumably indicating the presence of antithrombin

Sixteen hours after delivery (May 23 9 00 a.m) the platelet count was still low while the remaining values were normal Only in the next analysis (May 25, 9 00 a.m.) was the coagulation status completely normal as judged by the above criteria. In these tests fibrinolytic activity could be detected in the plasma s euglob-

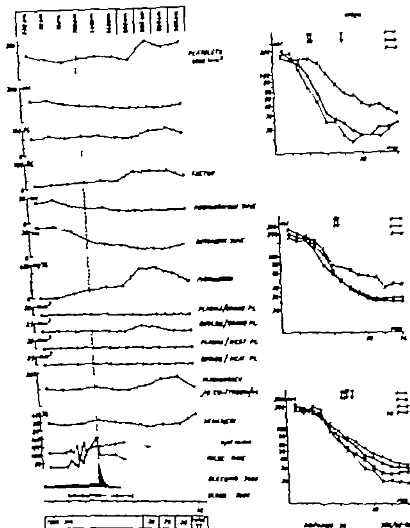


Fig. The variations in the concentration of the coagulation factors (platelet count, partial thromboplastin time (PTT) prothrombin-proconvertin (P-P) factor V prothrombin and thrombin times and fibrinogen concentration) in the content of fibrinolytic components (fibrinolytic activity in plasma and in iso-electrically precipitated plasma (euglobulins) measured upon standard fibrin plates and on heated plates and the plasminogen content) and in the haematocrit

T the ght of the figure the results of the two-stage TAT are given. The numbering of the curves corresponds with the numeration of the analyses at the bottom of the figure. The corresponding recalcification times are indicated by arrows.

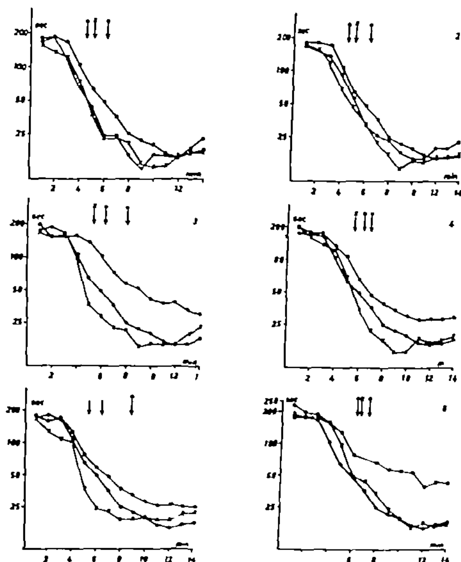


Fig 2. The three-stage TAT Each graph from no 1 to no 6 corresponds with that in the two-stage TAT in Fig. 1 ○——○ Two-stage TAT on normal human platelet-rich plasma. ●——● Two-stage TAT on the patient's plasma. x——x: The three-stage TAT with addition of 0·05 ml patient plasma to 0·20 ml normal human, platelet-rich plasma.

ulin fraction. This might indicate a moderate content of plasminogen activator which was without significant effect on plasminogen, the concentration of which was rising

The results of the two-stage TAT are also given in Fig 1 The two curves (nos. 1 and 2) showed a normal formation of plasma thromboplastin and thrombin although at that time the remaining coagulation factors were very defective. The recalcification times which were difficult to read as there was only a weak gritty precipitation due to lack of fibrinogen, were found to be shortened as compared with the values in normal parturient women (Skjodt and Albrechtsen, 1965) The following curve (no. 3) revealed decreased formation of plasma thromboplastin and thrombin together with a considerable prolongation of the recalcification time. The curves at the time of delivery and one hour later (nos. 4 and 5) showed renewed signs of increased thromboplastin activation and the recalcification times were shortened once again. In curve no 6 (three hours after delivery) a reduction in the thromboplastin activation again was evident, while the remaining curves (nos. 7 10) showed the values gradually returning to normal.

The results of the three-stage TAT are given in Figs. 2 and 3. The graphs numbered 1–10 correspond to the two-stage TAT graphs in Fig. 1 In each graph three curves are plotted. a) Two-stage TAT for normal human, platelet-rich plasma. b) Two-stage TAT on the patient s plasma identical with the curves in Fig. 1 c) Three-stage TAT here 0.05 ml patient plasma is added to 0 20 ml normal human, platelet rich plasma.

From graphs nos. 1–5 it is seen that the patient s plasma caused a stronger thromboplastin activation by addition to normal plasma, as the coagulation times were clearly shortened after an incubation time of three to four minutes. This acceleration manifested itself during the further progress of the process At the same time the recalcification times were considerably shortened in the incubation mixture

These changes lasted until one hour after delivery (graph no. 5) but three hours after the delivery (graph no 6) the clot promoting effect of the patient s plasma on normal plasma had ceased (graphs nos. 7–10)

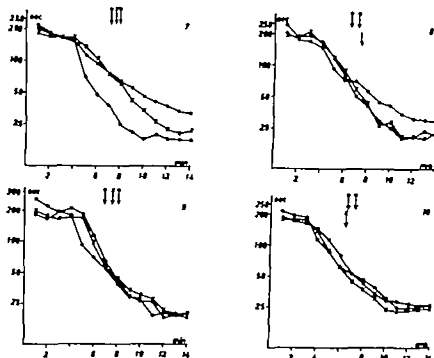


Fig. 3. Three-stage TAT. Each graph from no. 7 to no. 10 corresponds with that in the two-stage TAT in Fig. 1. For key see Fig. 2.

Table I. *The Thromboplastin Generation Screening Test (Hicks and Pitney) Expressed by Generation Factor (GF) at Various Times During the Course of the Investigation*

			GF				GF
1	May 22	8.30 a.m.	65	6	May 22	6.40 p.m.	55
2	May 22	9.30 a.m.	65	7	May 23	9.00 a.m.	60
3	May 22	2.30 p.m.	65	8	May 25	9.00 a.m.	65
4	May 22	3.40 p.m.	52	9	May 28	9.00 a.m.	65
5	May 22	4.40 p.m.	65	10	June 17	9.00 a.m.	48

The results of the thromboplastin generation screening test (Hicks and Pitney 1957) expressed as the generation factor (GF) are given in Table I. GF was distinctly prolonged in relation to the values in normal parturient and puerperal women at comparable times (49.4–55.7) (Skjødt, 1967). This indicates that the formation of plasma thromboplastin and thrombin were

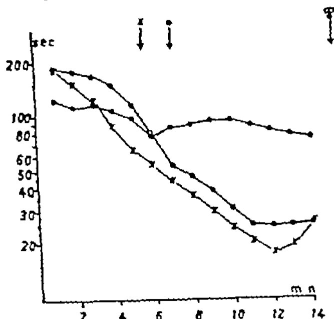


Fig. 4 Two-stage TAT on normal human, platelet-rich plasma. ● —● Two-stage TAT on uterine serum x x. Three-stage TAT with addition of 05 ml uterine serum to 0.20 ml normal human, platelet rich plasma.

decreased and represents a reduced content of the coagulation factors in the 1st phase. However in test 4 (May 23 3.40 p.m.) immediately after the delivery a transcient return of the thromboplastin generation to normal was seen. The GF did not become completely normal until 4 weeks post partum.

The haematocrit values are given in Fig. 1. The values were essentially reduced and were not found to be normal till 4 weeks after the delivery.

The results of the analyses of *uterine blood* collected immediately after the delivery of placenta were as follows: platelet count 8000/mml. P-P 19 %. Factor V 1.2 %. Prothrombin time and thrombin time were indefinite as is expected from the remaining values and the total lack of fibrinogen. No increased fibrinolytic activity was found and the plasminogen content equalled that in the peripheral blood at the same time.

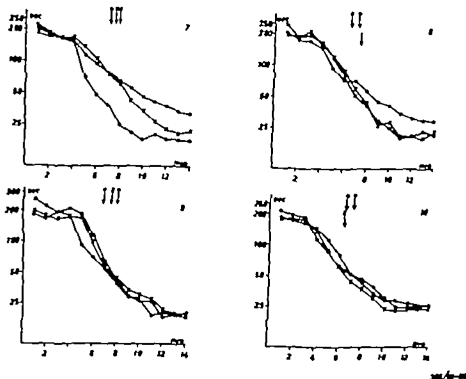


Fig 3. Three-stage TAT Each graph from no. 7 to no. 10 corresponds with that in the two-stage TAT in Fig. 1 For key see Fig 2.

Table I *The Thromboplastin Generation Screening Test (Hicks and Pitney) Expressed by Generation Factor (GF) at Various Times During the Course of the Investigation*

			GF				GF
1	May 22	8.30 a.m	65	6	May 22	6.40 p.m.	55
2	May 22	9.30 a m	65	7	May 23	9 00 a.m.	60
3	May 22	2.30 p.m	65	8	May 25	9 00 a.m.	65
4	May 22	3.40 p.m	52	9	May 28	9 00 a m	65
5	May 22	4.40 p m.	65	10	June 17	9 00 a m.	48

The results of the thromboplastin generation screening test (Hicks and Pitney 1957) expressed as the generation factor (GF) are given in Table I GF was distinctly prolonged in relation to the values in normal parturient and puerperal women at comparable times (49 4–55.7) (Skjodt, 1967) This indicates that the formation of plasma thromboplastin and thrombin were

formation of plasma thromboplastin or thrombin occurred, which accords with the fact that the coagulation factors normally are consumed during the spontaneous coagulation of blood. The three-stage TAT was performed by adding serum to the patient's own plasma which at this time coagulated normal. The serum caused activation of the coagulation system of the normal plasma. Only t 1 and t 14 were identical with the coagulation times of normal plasma at these points while the remaining coagulation times were reduced. Also the recalcification time was clearly shortened.

Discussion

In the first two analyses no fibrinogen was demonstrated in the blood, but the afibrinogenemia was not complete as it was possible to determine the recalcification time and the prothrombin time. This is possible only if fibrinogen is present in the plasma being analysed. However there was no solid clot formation, but only a weak, gritty precipitation as occurs with severe hypofibrinogenemia. The co-existent presence of anti-thrombin may explain the afibrinogenemia demonstrated and also the indefinite thrombin times.

On the basis of the results of the analyses of coagulation and fibrinolysis it might be reasonable to assume that the gross coagulation defect in the peripheral blood was caused by consumption of fibrinogen and several other coagulation factors by an activation of the coagulation process. The demonstrated activation of the fibrinolytic enzyme system was not of such a magnitude that a massive decomposition of fibrinogen and other coagulation factors, sensitive to plasmin could be expected. The low plasminogen values indicated that such an activation had taken place, possibly released by an activation of the coagulation process to reduce the extent of intravascular fibrin precipitation. The finding that the plasmin might be linked to the precipitated fibrin may possibly explain why no plasmin could be demonstrated by the fibrin plate method.

The results of the thromboplastin activation test point towards the fact that an activation of the coagulation process was primary

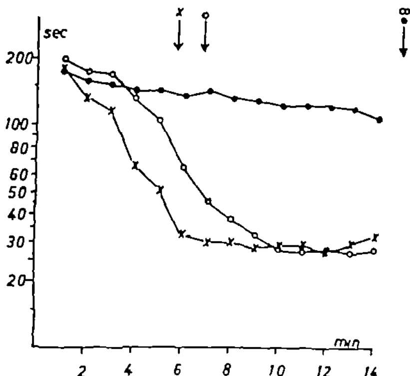


Fig 5 O——O Two-stage TAT on the patient s plasma four weeks after delivery ●——● Two-stage TAT on the patient s serum four weeks after delivery x——x Three-stage TAT with addition of 0.05 ml patient serum to 0 20 ml patient plasma four weeks after delivery

The results of the two-stage and three-stage TAT are given in Fig 4 From this it can be seen that no formation of plasma thromboplastin or thrombin took place and that the recalcification time was indefinite Furthermore it was disclosed that the uterine blood was able to accelerate the thromboplastin activation in normal plasma No shortening of t 1 was found, but the coagulation times measured in the remaining glass tubes were clearly shortened and the recalcification time was reduced.

The thromboplastin generation screening test (Hicks and Pitney 1957) confirmed the assumption of a greatly reduced content of coagulation factors of the 1 phase as the GF was very high (548)

Finally the two-stage TAT performed upon *serum* from the patient four weeks after the delivery (Fig 5) Practically no

formation of plasma thromboplastin or thrombin occurred, which accords with the fact that the coagulation factors normally are consumed during the spontaneous coagulation of blood. The three-stage TAT was performed by adding serum to the patient's own plasma which at this time coagulated normal. The serum caused activation of the coagulation system of the normal plasma. Only t 1 and t 14 were identical with the coagulation times of normal plasma at these points while the remaining coagulation times were reduced. Also the recalcification time was clearly shortened.

Discussion

In the first two analyses no fibrinogen was demonstrated in the blood, but the afibrinogenemia was not complete as it was possible to determine the recalcification time and the prothrombin time. This is possible only if fibrinogen is present in the plasma being analyzed. However there was no solid clot formation but only a weak, gritty precipitation as occurs with severe hypofibrinogenemia. The co-existent presence of anti-thrombin may explain the afibrinogenemia demonstrated and also the indefinite thrombin times.

On the basis of the results of the analyses of coagulation and fibrinolysis it might be reasonable to assume that the gross coagulation defect in the peripheral blood was caused by consumption of fibrinogen and several other coagulation factors by an activation of the coagulation process. The demonstrated activation of the fibrinolytic enzyme system was not of such a magnitude that a massive decomposition of fibrinogen and other coagulation factors, sensitive to plasmin, could be expected. The low plasminogen values indicated that such an activation had taken place, possibly released by an activation of the coagulation process to reduce the extent of intravascular fibrin precipitation. The finding that the plasmin might be linked to the precipitated fibrin may possibly explain why no plasmin could be demonstrated by the fibrin plate method.

The results of the thromboplastin activation test point towards the fact that an activation of the coagulation process was primary

The two-stage TAT revealed a course almost identical with the curves in another case of premature separation of placenta with marked hypofibrinogenemia (Skjodt 1967) Eight hours before the delivery an apparently normal formation of plasma thromboplastin and thrombin was found at the same time as the remaining analyses disclosed severe defects in the coagulation process (Fig 1) Then the thromboplastin activation descreased only to increase during the delivery itself These changes might indicate that clot promoting components generated in the patient s blood. However the two-stage TAT does not demonstrate readily the clot promoting components Furthermore the two-stage TAT implies that there is sufficient content of activatable coagulation factors in the patient s plasma.

On the other hand it is possible by using the three-stage TAT more readily to demonstrate the clot promoting components in the blood. In this modification of the test the result of the analysis is independent of the content of activatable coagulation factors in the patient s plasma The three-stage TAT confirmed the fact that clot promoting components existed in the patient s blood at the times when this was also indicated by the two-stage TAT When the two-stage TAT showed no signs of coagulation activity (Fig 1 curve 3) the three-stage TAT still disclosed marked acceleration of the thromboplastin activation in normal plasma (Fig 2 diagram 3) As the coagulation accelerating effect did not begin till 3–4 minutes after the recalcification of the incubation mixture it is reasonable to suppose that the clot promoting component was the serum thrombotic accelerator (STA) Thus by means of the three-stage TAT the clot promoting component STA could be demonstrated from eight hours before the delivery till one hour after

Neither the two-stage nor the three-stage TAT however can elucidate whether the STA originates from intravascular coagulation where during retraction the fibrin precipitated intravascularly yields serum to the circulating blood or whether serum from the retroplacental clot passes into the maternal circulation a process favoured by the strong contraction activity Even though there was no evidence of tissue thromboplastin as judged by absence of early acceleration of thromboplastin activation in

normal plasma this does not exclude the possibility of infusion of tissue thromboplastin. In experiments with animals it has been shown that large doses of tissue thromboplastin injected intra venously cannot be demonstrated in the blood. This may be due to the fact that tissue thromboplastin is consumed immediately during the intravascular activation of the coagulation process or that the tissue thromboplastin is removed in the reticulo-endothelial system (Albrechtsen and Brakman (personal com munication))

Attention is drawn especially to the brief drop in the blood pressure and the loss of consciousness some three hours prior to delivery This happened shortly after the infusion of oxytocin was started. It might be due to intravascular precipitation of fibrin resulting from passage of serum and tissue thromboplastin from the uterine cavity to the maternal circulation However this concept does not seem to be correct. No further increase in the coagulation accelerating activity of the blood occurred at this time. Furthermore the fibrinogen concentration was increasing, which makes consumption of fibrinogen by coagulation very unlikely The brief attack was rather due to the infusion of oxy tocin and the resulting reaction to pain.

As large amounts of clot were expelled from the uterus fol lowing delivery it is likely that intrauterine coagulation was responsible for the consumption of the coagulation factors in the circulating blood. In addition to this the strong uterine tone might very well have forced serum from the retroplacental hæmatoma into the maternal circulation. This together with the blood transfusions might have contributed to the maintenance of the circulat ing blood volume This may explain why the patient was not shocked despite the severe hæmorrhage, and the low hæmatocrit values support this opinion

An intravascular activation of the coagulation process due to tissue thromboplastin may also have been contributary even though no signs of tissue thromboplastin were found in the blood and even though no dyspnoea or cyanosis occurred as in obstetric shock The circulating STA caused hardly any further intra vascular activation of the coagulation mechanism, as the fibrinogen concentration increased during delivery This may be ex

plained by the fact that the patient was not shocked, and th
seems to agree with Wessler s opinion (1955) that the clo
promoting effect in serum only manifests itself in parts of th
circulatory system where stasis prevails.

The acceleration of the thromboplastin activation, as demon
strated by the two-stage and three-stage TAT was presumabl
caused by STA This view is supported by the fact that the three
stage TAT was normal four weeks after delivery at which tim
the patient s serum had a distinct clot promoting effect upon he
own plasma (Fig 5)

The analyses of the uterine blood confirm previous analyse
(Skjødt and Albrechtsen 1965) Thus it was demonstrate
that intrauterine coagulation took place and probably was cause
by tissue thromboplastin from placenta and decidua The proces
was extensive as the reduction in the content of coagulatio
factors was very marked. The uterine blood could not coagulate
and the blood" was presumably a mixture of serum and red cells
This was confirmed by the three-stage TAT where the uterin
serum caused marked acceleration of thromboplastin activation i
normal plasma This analysis also failed to demonstrate tissue
thromboplastin as the accelerating effect, characterized by early
onset did not occur Thus the coagulation defect in the periphera
blood seems largely to be caused by a consumption of fibrinogen
and other coagulation factors consequent upon the retroplacenta
coagulation

Serum from the large retroplacental clot may then have passed
into the maternal circulation where the coagulation status may
have deteriorated as the result of a haemodilution It is also
reasonable to suppose that tissue thromboplastin passes into the
circulating blood, where an intravascular activation of the coagu
lation process took place with later liberation of STA from intra
vascularly precipitated fibrin

In spite of the marked hypofibrinogenemia blood transfusions
only were given before the delivery of the child.

Infusion of human fibrinogen was avoided because of the risk
of tissue thromboplastin causing intravascular precipitation of
added fibrinogen (Albrechtsen and Skjødt 1964) Of
course, the infusion of blood would not be expected to correct

the coagulation defect, but the coagulation values nevertheless showed slight increases during treatment. It took some time before the coagulation conditions returned to normal. The blood transfusions were of value principally for effective shock prophylaxis which plays a decisive part in coagulation balance. As mentioned above stasis in the circulatory system is able to accentuate the action of STA. In addition shock very often leads to a major activation of the fibrinolytic enzyme system, with possibility of further deterioration of the coagulation status.

The STA still could be demonstrated in the blood two hours after delivery which agrees with Wessler's finding (1955) that the STA disappears from the blood about two hours after completion of coagulation activation. Thus the presence of the STA in the blood after delivery does not necessarily indicate continued activation of the coagulation The possibility of this kind of coagulative activation is slight and the danger of thromboplastin infusion must be regarded as insignificant after delivery

As the patient was not shocked the presence of STA in the blood would hardly have caused any intravascular precipitation of added human fibrinogen if this treatment was indicated after delivery However no such indication existed as the haemorrhage stopped shortly after delivery Treatment was continued with blood transfusions and 16 hours after delivery the fibrinogen concentration was 340 mg/100 ml. This reveals that fibrinogen is formed very quickly or given off very quickly from extravascular depots. Therefore fibrinogen treatment is not always necessary in cases of hypofibrinogenemia This is also important in relation to the risk of serum hepatitis (Cronberg, Belfrage and Nilsson, 1963)

SUMMARY

A case is presented of premature separation of the placenta with hypofibrinogenemia in the circulating blood. Coagulation analyses were performed regularly which besides the hypofibrinogenemia disclosed low concentrations of several other coagulation factors.

Among the methods of analysis used the thromboplastin activation test as described by Astrup and Ollendorff (1961) was

very valuable This test was performed in two-stages as well as in three-stages. Compared with the results of the remaining analyses of coagulation and fibrinolysis the results of these tests indicated the presence of a clot-promoting component, probably of the same character as the "serum thrombotic accelerator (STA) described by Wessler (1955) The presence of the "serum thrombotic accelerator" indicates an activation of the coagulation process. It is possible that this "serum thrombotic accelerator has passed into the maternal circulation with serum from the large retroplacental clot which was present in this patient. It might also originate from serum given off to the circulating blood from intravascular fibrin precipitation caused by tissue thromboplastin from placenta and decidua.

REFERENCES

Albrechtsen O K. and *Skjodt P* Acta obst. et gynec. scandinav *43* 179, 1964

Albrechtsen O K. and *Brakman P* personal communication

Astrup T and *Ollendorff P* Scand. J Clin. & Lab. Invest. *13* 377 1961

Astrup T and *Albrechtsen O K.* Fed. Proc. *23* 354 1964

Cronberg, S Belfrage S and *Nilsson I M* Lancet I 96 1963

Hicks N D and *Pitney W R.* Brit J Haemat. *3* 228 1957

McKay D G Disseminated Intravascular Coagulation Hoeber Medical Division Harper & Row New York Evanston and London, 1965 p. 179

Nilsen P A. Acta obst. et gynec. scandinav *42* 1963 Suppl. 2

Schneider C L. Ann N Y Acad. Sci 75, 634 1959

Skjodt P and *Albrechtsen O K.* Acta obst. et gynec. scandinav *44* 416 1965

Skjodt P Acta obst. et gynec. scandinav *46* 9 1967

Wessler S J Clin. Invest. *34* 647 1955

Received on May 15th, 1966

Skødt, Preben, Acta obst. et gynec. scandinav. 46, 90, 1967

From the State Maternity Hospital Aarhus (Professor M. Iversen) and the Blood Group Laboratory (F. Kissmeyer-Nielsen, M.D.) the Municipal Hospital Aarhus Denmark

INTRAUTERINE FŒTAL DEATH WITH HYPOFIBRINOGENEMIA

Coagulation Studies in a Case Treated with Heparin

BY

PREBEN SKJØDT

Coagulation disturbances in patients with prolonged intrauterine foetal death are very frequent. Thus Hodginson Thompson and Hodari (1964) state that hypofibrinogenaemia occurs in 25 per cent cases when the duration of foetal death is five weeks or more.

The cause of the coagulation defect has not yet been definitely determined. According to some authors consumption of the fibrinogen of the blood by an intravascular coagulation might explain the hypofibrinogenaemia (Weiner Reid, Roby and Diamond, 1950) and (Reid, Weiner and Roby 1953). Others thought that activation of the fibrinolytic enzyme system of the blood results in decomposition of the fibrinogen and of other coagulation factors (Moloney Egan and Gorman, 1949 Jackson, Hartman and Busby 1955 Jürgens and Beller 1959 Phillips Skrodelis and King, 1964). The third view is that the fibrinogen of the blood is precipitated as fibrin in the intervillous spaces in the placenta (Ashworth and Stouffer 1956 Soulier 1956 Stouffer and Ashworth, 1958 Little and Phillips 1962).

Among 11 cases of intrauterine foetal death lasting for more than five weeks the author found two cases with hypofibrinogenaemia (Skjødt, in prep.). One of these patients is of special interest as clot-promoting components were found in the blood

very valuable This test was performed in two-stages as well as in three-stages Compared with the results of the remaining analyses of coagulation and fibrinolysis the results of these tests indicated the presence of a clot promoting component, probably of the same character as the "serum thrombotic accelerator" (STA) described by Wessler (1955) The presence of the serum thrombotic accelerator indicates an activation of the coagulation process. It is possible that this "serum thrombotic accelerator has passed into the maternal circulation with serum from the large retroplacental clot which was present in this patient. It might also originate from serum given off to the circulating blood from intravascular fibrin precipitation caused by tissue thromboplastin from placenta and decidua

REFERENCES

Albrechtsen O K. and *Skjødt* P Acta obst. et gynec. scandinav *43* 129 1964
Albrechtsen O K. and *Brakman* P personal communication
Astrup T and *Ollendorff* P Scand J Clin. & Lab Invest. *13* 377 1961
Astrup T and *Albrechtsen* O K. Fed. Proc 23 354 1964
Cronberg S *Belfrage* S and *Nilsson* I M Lancet I 967 1963
Hicks N D and *Pitney* W R. Brit J Hemat. 3 228 1957
McKay D G Disseminated Intravascular Coagulation Hoeber Medical Division Harper & Row New York Evaston, and London 1965 p 179
Nilsen P A. Acta obst et gynec scandinav 42 1963 Suppl. 2
Schneider C. L. Ann N Y Acad. Sci 75 634 1959
Skjødt P and *Albrechtsen* O K Acta obst et gynec scandinav *44* 418 1965
Skjødt P Acta obst. et. gynec. scandinav *46* 19 96
Wessler S J Clin Invest. *34* 647 1955

Received on May 15th 1966

ing the following three days the dose was increased to 25,000 I.u. twice daily after which the fibrinogen concentration went up to 249 mg/100 ml.

During treatment extensive ecchymoses and bruises appeared round the injection sites.

On March 28 three days after the cessation of the heparin treatment, there were slight uterine contractions and transient moderate vaginal bleeding.

On the morning on March 29, there was renewed vaginal bleeding. At 1.30 p.m. a thick-walled sac was delivered containing macerated fœtus measuring 17 cm. The placenta contained in the wall of the ovisac was thin and degenerated. Only slight bleeding followed.

The uterine cavity measured 17 cm and some fœtid tissue was removed. At the same time there was a gush of fresh blood with two small clots totalling about 350 ml. There was no fall in the blood pressure and no respiratory distress. Blood transfusion was started at once, even though the bleeding stopped quickly after the intravenous administration of methergin 1 ml. After the infusion of 400 ml blood shivering occurred, and the transfusion was stopped accordingly. Later serologic investigation revealed leucocyte agglutinins in high titre which might explain the transfusion reaction.

After the heparin treatment the concentration of fibrinogen rose to 249 mg/100 ml as mentioned above. At the time of the abortion and the subsequent curettage the fibrinogen value dropped to 200 mg/100 ml, but by the following day the value had gone up to 330 mg/100 ml (Fig.)

The further course was without complications, with normal temperature pulse and blood pressure. The patient was discharged on April 1, 1965.

The grossly macerated fœtus showed no malformations. Microscopic examination of the placental tissue revealed distinct changes. The structure of the villus was completely changed, the villous epithelium had perished, there were diffuse fibrin deposits in the villi and almost all the intervillous spaces were filled with fibrinoid substance. Scattered organization of the fibrin was seen, with occasional calcification.

The tissue removed by curettage contained mucosa with fairly narrow glands, mostly without secretion, and decidual tissue with distinct inflammatory reaction. No placental tissue was found in the tissue removed (Prof. W. Munck M.D.)

Analytical Methods

The blood sampling procedure and the preparation of the samples were performed as described previously. The determination of haematocrit, platelet count, recalcification time, partial thromboplastin time (PTT), prothrombin-proconvertin (P-P), factor V, prothrombin time and thrombin time, concentration of fibrinogen and the measurement of fibrinolytic activity in the plasma and in iso-electrically precipitated plasma on standard fibrin-plates and on heat-treated plates, and the plasminogen determination were also car

indicating that an activation of the coagulation process had taken place. Coagulation analyses before, during and after treatment with heparin seem to show that the cause of the hypofibrinogenaemia was intravascular activation of the coagulation mechanism.

Case Report

J. no. 2115/64–65. 34-year-old gravida VI, para III, abortion 2. No hereditary tendencies to hæmorrhagic diathesis. During the preceding 15 years she had intermittent periods of depression. In 1961 partial gastrectomy was performed because of a peptic ulcer and in connection with the operation blood transfusions were given.

In 1952, 1955 and 1962 she had normal deliveries with no exceptional bleeding.

In 1953 she had a spontaneous abortion in the 3rd month, after which curettage was performed with only moderate bleeding.

In 1960 she had a missed abortion. Uterine evacuation was performed in the 5th month with only moderate bleeding.

After each pregnancy she was mentally extremely depressed and attended psychiatric departments. After the last delivery in 1963 the patient had a puerperal psychosis which was treated with psychotherapeutic drugs.

Her last regular menstrual period was on Aug. 17, 1964, six months before admission, but was followed by moderate bleeding on September 27.

In early November the uterus was enlarged to the size of a 10–12-week-old pregnancy. She had no complaints and needed no psychotherapeutic drugs during the pregnancy.

On Dec. 8, and during the subsequent months she felt foetal movements.

In mid-January 1965 the uterus hardly reached the umbilicus and no foetal heart sounds were heard.

In mid-February the uterus reached 3 cm below umbilicus and foetal heart sounds were still absent.

On March 5, the uterus corresponded in size to a pregnancy of 16 weeks duration.

On March 11, the fibrinogen concentration was 120 mg/100 ml, and because of this the patient was admitted to hospital on March 17, when the fibrinogen concentration was found to 133 mg/100 ml.

On March 18, the level was 144 mg/100 ml and on March 19, 121 mg/100 ml.

On the basis of Sherman and Middleton's information (1958) heparin treatment was commenced to inhibit any possible intravascular activation of the coagulation process.

From March 19 to 22, 25,000 i.u. of heparin was given subcutaneously at 8 a.m. Only a small increase in the fibrinogen concentration was noted. Dur-

(March 21) but otherwise it was unchanged. The concentrations of P P and factor V were unchanged, the prothrombin time was slightly prolonged and the thrombin time was much prolonged. The fibrinolytic activity in the euglobulin fraction was unchanged, measured on standard plates while the plasminogen values showed a definite increase.

During the next three days (March 23–25) 25.000 i.u. of heparin was administered at 8.00 a.m. and at 5.00 p.m. This intensified therapy resulted in marked changes in the coagulation status, which were also present the day after the cessation of the heparin therapy (March 26) The fibrinogen concentration rose to 249 mg/100 ml. The platelet count, previously 400 000/mml began to fall. The PTT was infinite The P P and factor V values decreased a little and the prothrombin times were slightly prolonged. The thrombin times were infinite. The fibrinolytic activity was unchanged, as determined by the fibrin-plate method, while the plasminogen content continued to increase considerably

On the following two days (March 27–28) the fibrinogen content dropped a little The platelet count fell further and the PTT became normal. P P was normal and factor V were only slightly reduced. Prothrombin and thrombin times were normal. The fibrinolytic activity in the euglobulin fraction, measured on standard plates, varied from 64–0 mm and at the same time the plasminogen content decreased somewhat.

On March 29. at 1 30 p.m. the patient had an abortion without noticeable bleeding On the same day at 5 00 p.m. curettage was performed, followed by a blood transfusion (400 ml) The fibrin ogen concentration had gone down a little and the platelet count was still low The P P and factor V concentrations were slightly reduced, while the remaining coagulation values were within the normal range The fibrinolytic activity in the euglobulin fraction measured on standard plates was almost unchanged, while the plasminogen content was reduced in relation to the values during the heparin treatment. The last three analyses (on March 30 April 1 and 8) showed gradual improvement of the coagulation status towards normal.

The haematocrit values were constantly around 40 vol %

Th thromboplastin generation screening test (Hicks and

ried out by methods described elsewhere (Skjødt and Albrechtsen, 1965)

The thromboplastin activation test as described by Astrup and Ollendorff (1961) and the thromboplastin generation screening test (Hicks and Pitney 1957) were carried out as described previously (Skjødt and Albrechtsen 1965 and Skjødt, 1967)

In these publications the technical procedure of these analyses was reviewed. At the same time a more detailed description was given of the principles of the thromboplastin activation test (TAT) two-stage as well as three-stage. Finally a three-stage in vitro experiment was made in order to correlate the coagulation accelerating effect found in human serum and in tissue thromboplastin (ROCHE)

Results

The results of the coagulation and fibrinolytic analyses in the patient are shown in Fig 1 The treatment with heparin and blood also is detailed. The first analysis was made on March 11 about 8 weeks after the intrauterine fœtal death was suspected and nearly three weeks before the abortion The fibrinogen concentration was 120 mg/100 ml The platelet count was slightly reduced, PTT P P and factor V were within the normal range while the prothrombin time and the thrombin time were slightly prolonged. No fibrinolytic activity was present in the plasma when measured neither on standard fibrin plates or on heat treated fibrin plates In iso-electric precipitated plasma (euglobulins) activity was found on standard plates indicating the presence of plasminogen activators but absence of activity on heated plates indicated a lack of plasmin The plasminogen content was reduced as compared with normal non pregnant women (Skjødt and Albrechtsen 1965)

Six days later on March 17 the fibrinogen concentration was still low 133 mg/100 ml but the other factors showed no significant changes. The same conditions were seen 24 hours later (March 18)

During the following four days (March 19–22) the patient daily received 25 000 I u. of heparin subcutaneously In this period the fibrinogen concentration increased and on March 22 a concentration of 168 mg/100 ml was measured The platelet count also increased The PTT was greatly prolonged for one day only

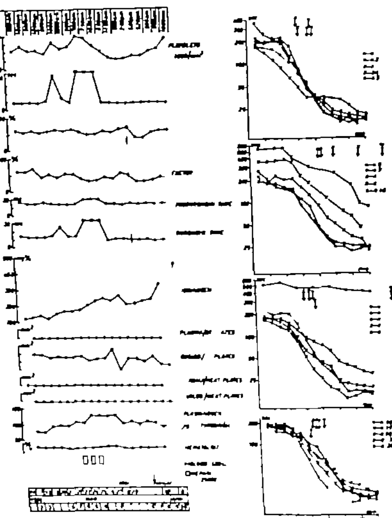


Fig. Variations in the concentration of the coagulation factors (platelet count, partial thromboplastin time (PTT), prothrombin-proconvertin (P-P), factor V, prothrombin and thrombin times and fibrinogen) and in the fibrinolytic activity in plasma and in iso-electrically precipitated plasma (englobulins) on standard plates and on heat treated plates and the plasminogen content related to the treatment.

T the right of the figure the two-stage TAT is shown. The numbering of the curves corresponds with the numeration of the analyses given at the foot of the figure. The corresponding recalcification times are indicated by arrows.

Table I. *The Thromboplastin Generation Screening Test (Hicks and Pitney) Expressed by Generation Factor (GF)*

No.	Date	Time	GF	No.	Date	Time	GF
1	March 11	9.00 a.m.	96	11	March 26	10.00 a.m.	226
2	March 17	10.00 a.m.	72	12	March 27	8.00 a.m.	53
3	March 18	9.00 a.m.	84	13	March 28	11.00 a.m.	66
4	March 19	10.00 a.m.	44	14	March 29	9.00 a.m.	48
5	March 20	8.00 a.m.	60	15	March 29	2.40 p.m.	40
6	March 21	10.00 a.m.	90	16	March 29	5.05 p.m.	56
7	March 22	10.00 a.m.	70	17	March 29	5.20 p.m.	48
8	March 23	9.00 a.m.	60	18	March 30	9.00 a.m.	52
9	March 24	9.00 a.m.	600	19	April 1	9.00 a.m.	44
10	March 25	7.50 a.m.	700	20	April 8	10.00 a.m.	72

Pitney 1957) is expressed by generation factors (GF). The results are stated in Table I. The tests nos. 1–3 illustrate the conditions before the heparin treatment, where the increased GF probably indicates reduced content of some of the factors of the first coagulation phase. The tests nos. 4–8 show GF during daily administration of 25.000 i.u. of heparin. GF varied, but apart from test no. 4 the values were increased compared with the normal non-pregnant state. Thus in 31 normal women GF was found to be 55.4 with a standard deviation of 17.1 and a standard error of the mean of 3.7 (Skjødt, 1967). In the tests nos. 9–11 GF was very much increased during the treatment with 25.000 i.u. of heparin twice daily. The following values were within the normal range.

The two-stage TAT is detailed on Fig. 1. The thromboplastin activity was found to be within the normal range in the analyses before and during the treatment with heparin 25.000 i.u. daily (the curves nos. 1–7).

During the intensive treatment with 25.000 i.u. of heparin twice daily a progressive flattening of the curves was found together with a marked prolongation of the recalcification times.

The three-stage TAT performed upon the samples nos. 2–20 are set down in *Figs. 2, 3 and 4. In each graph three curves are* drawn: a) The two-stage TAT on the patient's platelet-containing plasma identical with the curves on Fig. 1. b) The two-stage

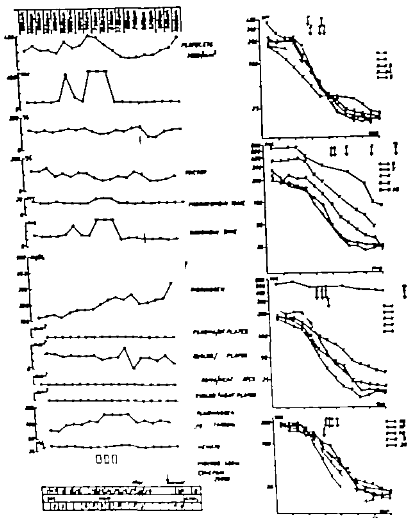


Fig. Variations in the concentration of the coagulation factors (platelet count, partial thromboplastin time (PTT) prothrombin-proconvertin (P-P) factor V prothrombin and thrombin times and fibrinogen) and in the fibrinolytic activity in plasma and in iso-electrically precipitated plasma (euglobulins) on standard plates and on heat-treated plates and the plasminogen content related to the treatment.

T the right of the figure the two-stage TAT is shown. The numbering of the curves corresponds with the numeration of the analyses given at the foot of the figure. The corresponding recalcification times are indicated by arrows.

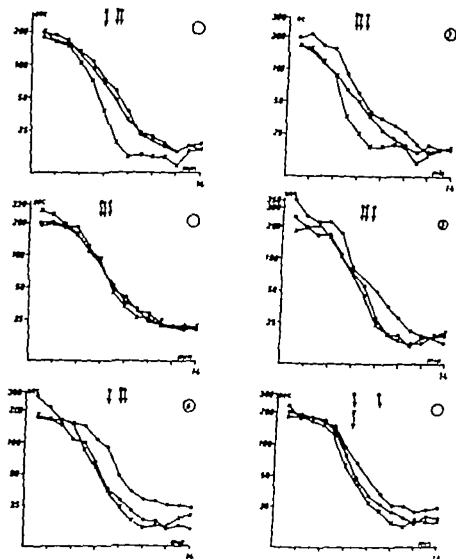


Fig. 2. The thromboplastin activation test (three-stage TAT) performed upon the patient's plasma. In each graph three curves are plotted. ● —— ● = two-stage TAT on the patient's plasma. ○ —— ○ = two-stage TAT on normal human platelet-rich plasma. x —— x = three-stage TAT: patient plasma (0.05 ml) + normal human platelet-rich plasma (0.20 ml). Each of the graphs from nos. 2–7 corresponds with those of the two-stage TAT in Fig. 1.

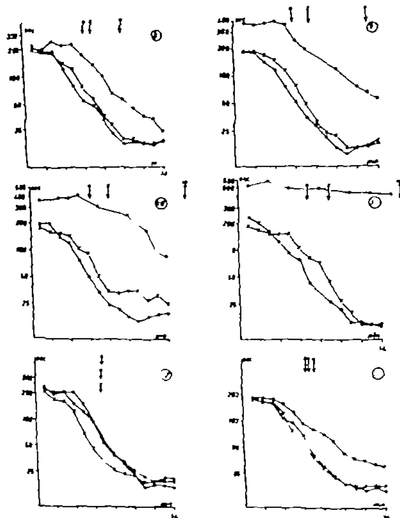


Fig. 3 The thromboplastin activation test (three-stage TAT) performed upon the patient plasma. Graphs nos. 8–13. For key see Fig. 2.

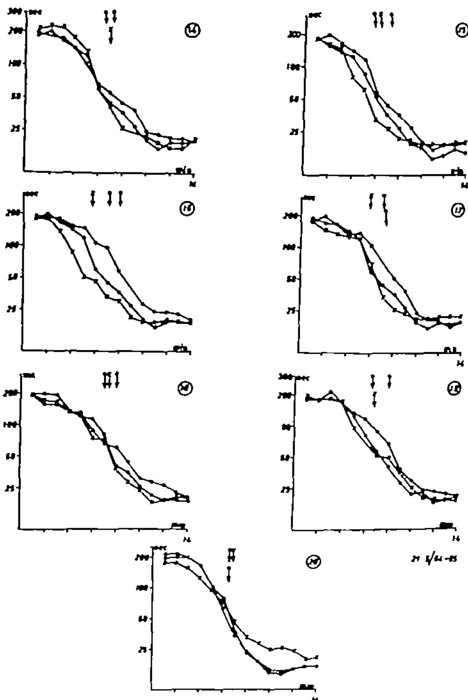


Fig. 4. The thromboplastin activation test (three-stage TAT) performed upon the patient's plasma. Graphs nos. 14–20. For key see Fig. 2.

TAT determined on normal human, platelet-rich plasma c) The three-stage TAT with the patient's plasma added to normal human platelet-rich plasma.

Apart from the analyses nos. 14–17 (Fig 4) the human plasma came from 15 normal women. The deviations of the two-stage TAT determinations in these women corresponded to those found by Astrup and Ollendorff (1961) in similar investigations in a single patient on seven occasions through a period of 40 days.

By using the same normal plasma sample for determination of the three-stage TAT in three cases it was found that 8 hours storage in an ice-bath caused only negligible changes in the thromboplastin activation.

Thus the results of the three-stage TAT on the different days during the investigation period should neither vary by the use of normal plasma from different persons nor vary if the same normal plasma sample is used within the first eight hours after the drawing of the blood sample

Before the heparin treatment the patient's plasma caused an acceleration of the formation of plasma thromboplastin and thrombin in normal plasma (Fig. 2, graphs 2 and 3) This could be demonstrated 4–5 minutes after the recalcification of the incubation mixture

During the therapy with heparin in doses of 25,000 i.u. daily the acceleration of thromboplastin activation was absent in normal plasma but the recalcification times in normal plasma with patient plasma added were prolonged (Fig 2 graphs nos. 4–7)

During the heparin treatment with 25,000 i.u. twice daily the addition of the patient's plasma to normal plasma produced a marked prolongation of the coagulation and recalcification times (Fig 3, graphs nos. 8–11)

Two days after the cessation of the heparin therapy there were again slight signs of acceleration of the thromboplastin activation (Fig. 3, graph 12) but the following day this tendency had disappeared (graph 13)

Scarcely six hours before the abortion there were no signs of accelerated activation of the coagulation (Fig 4 graph 14) After the spontaneous abortion there were renewed signs of accelerated

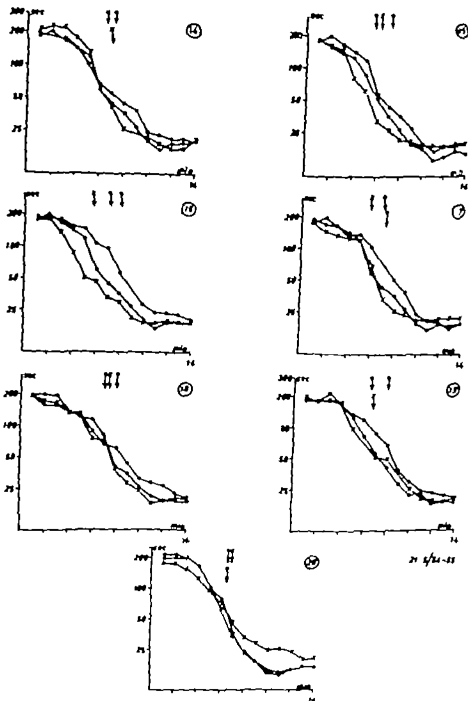


Fig. 4. The thromboplastin activation test (three-stage TAT) performed upon the patient's plasma. Graphs nos. 14–20. For key see Fig. 2.

passage into the maternal circulation, cause intravascular coagulation with consumption of the fibrinogen of the blood. Jürgens and Beller (1959) and Kraut and Körbel Enkhardt (1958) are under the impression that the fibrinolytic tissue activator might be liberated by the maceration of the foetus and that this might pass into the circulating blood, where plasmin is created after activation of the fibrinolytic enzyme system. Thus decomposition of the fibrinogen of the blood and other coagulation factors might explain the coagulation defect. Finally Soulier (1956) Ashworth and Stouffer (1956) and Little and Phillips (1962) state that hypofibrinogenaemia might be due to the deposition of the blood fibrinogen in the placenta as fibrin, especially in the intervillous spaces.

In the present paper attempts have been made to illustrate the aetiologic factors by analyses of coagulation factors and fibrinolysis before during and after treatment with heparin.

Prior to the heparin treatment the analyses disclosed hypofibrinogenaemia together with signs of activation of the fibrinolytic enzyme system of the blood, as evidenced by a reduced plasminogen content. There was also a slight reduction in the platelet count and signs of decreased concentration of the coagulation factors of the first phase. This is illustrated by the thromboplastin generation screening test (Hicks and Pitney) which showed increased GF indicating reduced formation of plasma thromboplastin and thrombin. The remaining coagulation factors were within the normal range

The results of these analyses do not exclude activation of the coagulation process of the blood apart from the activation of the fibrinolytic system. Attempts are made to illustrate this problem by means of the thromboplastin activation test (Astrup and Ollendorff 1961)

Contrary to the Hicks and Pitney test the two-stage TAT showed that the formation of the plasma thromboplastin and thrombin was normal (Fig. 1 curves nos. 1–3) This discrepancy might indicate the presence of components accelerating coagulation in the patient's blood, demonstrable by the more sensitive thromboplastin activation test, but not by the thromboplastin generation screening test.

coagulation (graph 15) which could be demonstrated 2–3 minutes after and, later 15 minutes after the abortion (graphs 16 and 17)

Analyses performed after one two and seven days (graphs nos. 18–20) revealed no signs of accelerated thromboplastin activation

Supplementary Experiment

These results indicate definite changes in coagulation status during heparin treatment. The increase of 95 per cent in the fibrinogen concentration was especially remarkable so was the considerable rise in the plasminogen content and the moderate increase in the platelet count. Besides a marked decrease was demonstrated in the thromboplastin activation in the two-stage and three-stage TAT

To illustrate the influence of circulating heparin on the results of analytic methods used here coagulation status was assessed during and after administration of heparin 25 000 i u. twice daily for 48 hours in a normal non pregnant woman. Before treatment normal coagulation conditions were found. During the heparin therapy the fibrinogen concentration rose from 230 mg/100 ml to 290 mg/100 ml, an increase of 26 per cent. The plasminogen content showed no definite changes but the platelet count decreased slightly

The two-stage TAT disclosed reduced formation of plasma thromboplastin and thrombin and the three-stage TAT revealed a decreasing thromboplastin activation equivalent to that in the patient with intrauterine foetal death The PTT and the thrombin times were infinite while the P P and factor V were reduced and the prothrombin time prolonged, which also corresponds with the conditions found in the patient.

Discussion

The cause of the coagulation defect in patients with intrauterine foetal death remains uncertain Reid and Diamond (1953) and Schneider (1954) think that tissue thromboplastin from the macerated foetus and the degenerated placenta might, after

passage into the maternal circulation cause intravascular coagulation with consumption of the fibrinogen of the blood. Jürgens and Beller (1959) and Kraut and Körbel Enkhardt (1958) are under the impression that the fibrinolytic tissue activator might be liberated by the maceration of the foetus and that this might pass into the circulating blood, where plasmin is created after activation of the fibrinolytic enzyme system. Thus decomposition of the fibrinogen of the blood and other coagulation factors might explain the coagulation defect. Finally Soulier (1956) Ashworth and Stouffer (1956) and Little and Phillips (1962) state that hypofibrinogenaemia might be due to the deposition of the blood fibrinogen in the placenta as fibrin, especially in the intervillous spaces.

In the present paper attempts have been made to illustrate the aetiologic factors by analyses of coagulation factors and fibrinolysis before during and after treatment with heparin.

Prior to the heparin treatment the analyses disclosed hypofibrinogenaemia together with signs of activation of the fibrinolytic enzyme system of the blood, as evidenced by a reduced plasminogen content. There was also a slight reduction in the platelet count and signs of decreased concentration of the coagulation factors of the first phase. This is illustrated by the thromboplastin generation screening test (Hicks and Pitney) which showed increased GF indicating reduced formation of plasma thromboplastin and thrombin. The remaining coagulation factors were within the normal range.

The results of these analyses do not exclude activation of the coagulation process of the blood apart from the activation of the fibrinolytic system. Attempts are made to illustrate this problem by means of the thromboplastin activation test (Astrup and Ollendorff 1961)

Contrary to the Hicks and Pitney test the two-stage TAT showed that the formation of the plasma thromboplastin and thrombin was normal (Fig. 1 curves nos. 1–3) This discrepancy might indicate the presence of components accelerating coagulation in the patient's blood, demonstrable by the more sensitive thromboplastin activation test, but not by the thromboplastin generation screening test.

This possibility was confirmed by the performance of the three-stage TAT Fig 2 graphs 2 and 3 show how the addition of the patient's plasma to the system caused acceleration of thromboplastin activation in normal plasma The demonstration of clot-promoting components in the patient's blood may be an indication of the fact that an activation of the coagulation process took place

The curves are characteristic of the presence of "serum thrombotic accelerator" (STA) in the blood as the accelerating effect did not begin till after 4 minutes. On the other hand the progress of the three-stage TAT did not indicate the existence of tissue thromboplastin in the patient's blood as the presence of the coagulation accelerating effect, which is characterized by a very early onset could not be shown. It is still possible that tissue thromboplastin eventually passed into the maternal circulation, where it might have caused a transient intravascular coagulation with precipitation of the fibrinogen of the blood as fibrin The difficulty of demonstating tissue thromboplastin in such a case might be due to the fact that it is removed at once possibly in the reticulo-endothelial system Thus Albrechtsen and Brakman (*personal communication*) *produced intravascular* coagulation in experiments with animals by intravenous injection of large doses of tissue thromboplastin without being able to demonstrate *its presence in the arterial blood.*

Therefore the STA might possibly have been generated as a result of an intravascular activation of the coagulation process caused by tissue thromboplastin. Serum from intravascularly precipitated fibrin might later have passed into the circulating blood. The STA in this might then have caused the acceleration of the thromboplastin activation in normal plasma However the STA might also originate from serum expelled from the diffuse intervillous fibrin precipitation in the placenta

It is important to emphasize that the presence of STA in the blood merely shows that an activation of the coagulation process took place and that STA does not necessarily produce an intravascular activation of this process despite its coagulation accelerating effect. Thus Wessler (1955) showed that this effect only manifests itself in the parts of the circulatory system where

stasis prevails. In the present case there was no reason to suppose that such a stasis was present, which seems to make further activation by STA unlikely

It cannot be decided whether the hypofibrinogenaemia originated from intravascular coagulation caused by tissue thromboplastin or because of intraplacental fibrin precipitation. As activity was measured in the euglobulin fraction of the plasma on untreated fibrin plates only as free plasmin did not occur and as at the same time the plasminogen content was considerably reduced, it must be supposed that the created plasmin was linked to the precipitated fibrin. This supports the theory of intravascular activation of the coagulation system, as this activation might activate secondarily the fibrinolytic system. But it seems unlikely that an intrauterine precipitation of fibrin should cause activation of fibrinolysis in the circulating blood.

Among the coagulation disturbances considered only the hypofibrinogenaemia is a feature in common with patients with premature separation of the placenta. While the coagulation defect in this complication of pregnancy is often characterized by thrombocytopenia and considerable reduction in the concentrations of prothrombin-proconvertin and factor V and much prolonged prothrombin and thrombin times all these factors were found to be within the normal range in the patient with intrauterine foetal death. This is probably explained by the protracted nature of intrauterine foetal death as opposed to the acute defibrination in patients with premature separation of the placenta. The gradual development gives an opportunity for regeneration of the coagulation factors in equilibrium with their consumption. The fact that hypofibrinogenaemia resulted in the present case despite this possibility might be explained by the relatively long turnover period of fibrinogen.

Heparin inactivates thrombin and inhibits the transformation of the prothrombin to thrombin (Douglas 1962) As at the same time it blocks the thromboplastin activity (Marbet, Studer and Winterstein 1954) heparin ought to be valuable in the treatment of a defibrination syndrome due to intravascular activation of the coagulation process. In one case of intrauterine foetal death with hypofibrinogenaemia Sherman and Midd-

leton (1958) used heparin with success to inhibit intravascular coagulation.

In the present case the heparin dosage of 25.000 i.u. twice daily resulted in marked changes in the coagulation status. The Hicks and Pitney test (Table I) as well as the two-stage TAT (Fig 1) clearly disclosed decreasing generation of plasma thromboplastin and thrombin The three-stage TAT (Fig 3 graphs nos. 8–11) revealed that the patient s blood inhibited thromboplastin activation in normal plasma whereas before treatment there was an acceleration. It cannot be concluded from this that the infused tissue thromboplastin was blocked, as the inhibition demonstrated equalled that shown in the supplementary experiment where a normal person was given heparin. The changes in the two-stage TAT as in the three-stage have to be taken as an indication of a heparin effect. The same applies to the moderate decrease of P P% factor V % the prolonged prothrombin times the in definite values of the PTT and the thrombin times Especially interesting are the changes in the fibrinogen content in the blood, in the platelet count and the increase of the plasminogen content (Fig 1) as these changes are not caused by the heparin.

As the fibrinogen concentration increased without simultaneous administration of blood or of human fibrinogen it is reasonable to suppose that the hypofibrinogenæmia was caused by intra vascular coagulation for inhibition of coagulation activation will result in decreased consumption of fibrinogen. The increasing platelet count might also be explained by this inhibition, as activation of the coagulation process causes *thrombocytopenia* (Koller 1961) The considerable increase in the plasminogen content indicates a gross reduction of fibrinolysis activation which may be reasonably explained by the inhibition of the intravascular coagulation The fibrinolytic provoking factor had then vanished. This agrees with Bekarda s (1962) opinion that heparin in hibits fibrinolysis by counteracting hypercoagulability Yet it cannot be excluded that heparin directly inhibited fibrinolytic activity Thus Nilsson Bielawiec and Björkman (1964) showed that heparin has a strongly inhibiting effect upon fibrin olytic activators.

In the supplementary experiment the fibrinogen concentration

was increasing during the heparin treatment, while the platelet count and the plasminogen values revealed no significant changes. As the heparin treatment here was briefer than in the patient it is possible that more marked changes in the coagulation and fibrinolytic components might have occurred if treatment had been continued.

After the cessation of the heparin effect in the patient the three-stage TAT disclosed a transient increase in coagulation activity although this was weaker than before heparin treatment (Figs. 3 and 4 graphs nos 12–17) Considering the simultaneous reduction in the platelet count, the decrease in P-P % and in the factor V concentration and the tendency towards further decrease in the fibrinogen concentration the results of the three-stage TAT might indicate a recurrence of intravascular activation of the coagulation process. The simultaneous decrease in the plasminogen content disclosed that the fibrinolytic system had been reactivated (Fig. 1 analyses nos. 12–17) These changes were most marked at the time of evacuation of the uterus (Fig 1 analyses 16 and 17) This might be due to the fact that the intrauterine manipulations caused further passage of factors activating coagulation into the maternal circulation.

Administration of heparin was started primarily in order to elucidate the cause of the development of the coagulation defect in relation to studies of coagulation and fibrinolysis. During this time the increasing fibrinogen concentration to normal levels indicates an inhibition of the increased coagulation activity However it would not be advisable to administer heparin routinely especially because of the danger of haemorrhage. Therefore a change in the usual principles of examination and treatment in cases of intra uterine foetal death is not recommended. When the diagnosis is certain as judged by cessation of uterine growth cessation of foetal movements, absent foetal heart sounds and eventually by X ray examination these patients ought to be followed by weekly fibrinogen determinations. Evacuation of uterus is advised before the fibrinogen concentration has dropped below the critical level of 150 mg/100 ml If there is hypofibrinogenaemia the patient may have to be treated with blood transfusions before evacuation of uterus. If this is followed by a profuse haemorrhage treatment

with human fibrinogen may be initiated. It is important to post pone fibrinogen treatment till after the evacuation as at this moment there is only a poor risk of the passage of tissue thromboplastin to the maternal circulation with resulting danger of intra vascular precipitation of the transfused fibrinogen

SUMMARY

An account is given of a case of intrauterine fœtal death with hypofibrinogenæmia The cause of this is elucidated by investiga tions on coagulation and fibrinolysis conditions before during and after the administration of heparin

The results of these investigations indicated that the coagula tion defect was caused by intravascular activation of the coagula tion process Thus before as well as after the heparin therapy there were signs of the presence of components accelerating coa gulation in the peripheral blood. During the heparin therapy there was an increase in the fibrinogen concentration in the platelet count and in the plasminogen content most likely due to an inhibition of the intravascular coagulation. This supports the assumption that an intravascular coagulation activation ex isted.

Even if the heparin treatment caused a significant increase in the fibrinogen content up to an adequate level this treatment of the coagulation defect in patients with intrauterine fœtal death is not recommended. Blood transfusion alone is indicated until the uterus is evacuated. Fibrinogen may be given after the evacua tion of uterus when the risk of the passage of tissue thromboplastin to the maternal circulation has been eliminated

REFERENCES

Albrechtsen O K. and *Brakman P* personal communication

Ashworth C T and *Stouffer J G* Am. J Clin Path. 26 1031 1956

Astrup T and *Ollendorff P* Scand. J Clin. & Lab Invest. 13 377 1961

Beberda B New Istanbul Contr Clin. Science 5, 186 1962

Douglas A. S Anticoagulant Therapy Blackwell Scientific Publications Oxford, 1962, pp 41 and 113

Hicks N D and *Pitney W R* Brit J Hæmat. 3 228 1957

Hodgkinson C. P *Thompson* R. J and *Hodari* A. A. Clinical Obstetrics and Gynecology Hoeber Medical Division, vol 7 349, 964
Jackson D P *Hartman* R. C. and Busby T Obst. & Gynec. 5 223 953
Jürgens J., and *Beller* F K. Klinische Methoden der Blutgerinnungsanalyse Stuttgart, 1959
Koller F Therapie Der Hämorrhagischen Diathesen, J Frei und J Jürgens. Stuttgart, Schattauer 196 p 3
Kraut H and *Körbel-Eckhardt* R. Leistungen und Ergebnisse der neuzeit lichen Chirurgie Stuttgart, 958
Little W A. and *Phillips* L. L. Am. J Obst. & Gynec. 84 421 96
Marbet R., *Studer* A., and *Winterstein* A. Wirkung von Protamin auf die Blutgerinnung. In Thrombose und Embolie I. Internat Tagung, Basel, 954
Moloney W C. *Egan* W J and Gorman A. J New England J Med 240 598 949
Nilsson I M. *Bielawiec* M., and *Björkman* S. E. Scand. J Haemat. 73, 1964
Phillips L. L *Skrodelis* V and *King*, T A. Am J Obst. & Gynec. 89 903, 964
Reid D E and *Diamond* L. K Am. J Obst & Gynec. 66 500, 953
Reid, D. E., *Weiner* A E and *Roby* C. C Am. J Obst. & Gynec. 66 590 953
Schneider C L Obst. & Gynec 4 273, 1954
Sherman E., and *Middleton* E. B Maryland Med. J 7 300 958
Skjødt P and *Albrechtsen* O K Acta obst et gynec. scandinav 44 416 965
Skjødt P Acta obst et gynec. scandinav 46 9 967
Skjødt P in prep
Soulier J P V Internat Congr Haematology Boston, 956
Stouffer J G and *Ashworth* C T Am J Obst. & Gynec. 75 407 958
Weiner A E. *Reid* D E., *Roby* C C and Diamond, L. K. Am. J Obst. & Gynec 60 5 950
Wessler S J Clin Invest. 34 647 955

Received on May 5th 966

Amris, C. J. and Starup J. Acta obst. et gynec. scandinav. 46, 78, 1967
From the Department of Clinical Chemistry Rigshospitalet (Professor P Astrup) University of Copenhagen and the Department of Gynaecology and Obstetrics (E. Østergaard M.D.) Frederiksberg Hospital Copenhagen Denmark

THE COAGULATION MECHANISM IN ORAL CONTRACEPTION

BY

C. J AMRIS AND J STARUP

During recent years oestrogen-gestagen combinations have been used widely both as oral contraceptives and in the treatment of menstrual irregularities. Several reports of thromboembolic episodes occurring during such hormone therapy (Jordan 1961 Mc.Intyre *et al.* 1962 Minogue *et al* 1963 Schatz *et al.* 1964) have aroused interest in the possible effects of gestagens and oestrogens on the hæmostatic mechanism

It has been established in many investigations that orally active gestagens or combinations of gestagens and oestrogens cause changes in the hæmostatic balance but the reports have been at variance with regard to the details of these changes. The majority of authors however have observed an increase in the concentration of some of the coagulation components which are also known to be elevated during pregnancy These investigations have been based either on short term studies (Brehm 1964 Egeberg and Owren 1963 Miller *et al* 1965 Phillips *et al* 1961 Spittel *et al* 1963) or on mean values of determinations on a few occasions before and during treatment with oral contraceptives (Donayre and Pincus 1965 Hougie *et al* 1965 Margulis *et al* 1965 Pilgeram 1964 Powell *et al* 1965 Rapaport 1962) In contrast to these reports Sobrero *et al* 1963 found all hæmostatic components to be within normal limits during treatment with norethindrone + mestranol.

Table I. *Normal Range of the Tests Performed in this Investigation*

Test	Normal Range
Whole blood clotting time, glass	6—1 min.
plastic	15—25 min.
Prothrombin consumption test (*Biggs and Macfarlane* 196 modified)	0—30 per cent
Recalcification time in citrated plasma	65—225 sec.
Thrombin generation test (*Ollendorff* 960)	—
Thromboplastin screening test (Hicks and Pitney 1957 modified)	—
Bleeding time (Duke)	≦5 min.
Platelets (direct count undil. plasma)	50000—400000/μl
Thromboplastin time, citrated plasma (using human brain thromboplastin)	index: $\frac{\text{normal}}{\text{patient}}$ × 00
Factors II+VII (*Owren and Aas* 1951)	80— 20 per cent
Factor V (*Wolf* 1953)	80—120 per cent
Factor VIII (*Nilsson et al.* 957)	60— 60 per cent
Fibrinogen (*Jacobsson* 955 modified by *Nilsson and Olow* 962)	0.2—0.4 g/ 00 ml
Plasma thrombin time	9— 2 sec.
Plasminogen (*Astrup* 966)	70—120 per cent
Euglobulin clot lysis time (*Nilsson and Olow* 196)	> 20 min. (mean: 300 min.)

In order to reveal the close relation between the haemostatic changes and the duration of treatment extensive coagulation studies were carried out at short intervals in 4 women with normal menstrual function before during, and after cyclical treatment with Delpregnin® (each tablet of Delpregnin contains 5 mg of megestrol acetate + 0.1 mg of mestranol)

Materials and Methods

Two groups of patients were studied. The first group consisted of 4 women with normal menstrual function who were respectively 23, 33, 38 and 44 years old. They were treated cyclically with Delpregnin for contraceptive purposes and received 1 tablet daily from day 5 to day 24 in the cycle. In all 4 patients coagulation studies were carried out 2 or 3 times during a control

Amris, C. J and Starup J Acta obst. et gynec scandinav 46, 7* 967

From the Department of Clinical Chemistry Rigshospitalet (Professor P Astrup) University of Copenhagen and the Department of Gynaecology and Obstetrics (E. Ostergaard M.D) Frederiksberg Hospital Copenhagen Denmark

THE COAGULATION MECHANISM IN ORAL CONTRACEPTION

BY

C. J. AMRIS AND J STARUP

During recent years œstrogen-gestagen combinations have been used widely both as oral contraceptives and in the treatment of menstrual irregularities. Several reports of thromboembolic episodes occurring during such hormone therapy (Jordan 1961 Mc.Intyre *et al* 1962 Minogue *et al.* 1963 Schatz *et al.* 1964) have aroused interest in the possible effects of gestagens and œstrogens on the hæmostatic mechanism.

It has been established in many investigations that orally active gestagens or combinations of gestagens and œstrogens cause changes in the hæmostatic balance but the reports have been at variance with regard to the details of these changes. The majority of authors however have observed an increase in the concentration of some of the coagulation components which are also known to be elevated during pregnancy These investigations have been based either on short term studies (Brehm 1964 Egeberg and Owren 1963 Miller *et al* 1965 Phillips *et al* 1961 Spittel *et al* 1963) or on mean values of determinations on a few occasions before and during treatment with oral contraceptives (Donayre and Pincus 1965 Hougie *et al* 1965 Margulis *et al* 1965 Pilgeram, 1964 Powell *et al* 1965 Rapaport, 1962) In contrast to these reports Sobrero *et al* 1963 found all hæmostatic components to be within normal limits during treatment with norethindrone + mestranol.

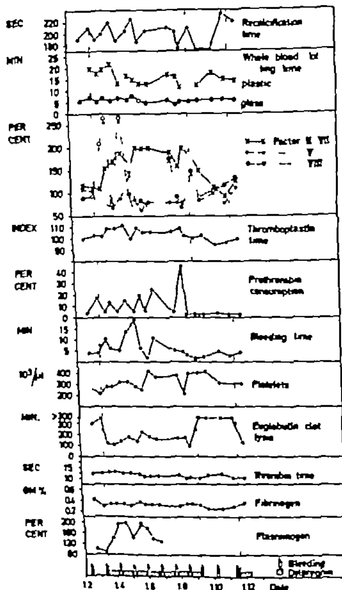


Fig Changes in the hemostatic mechanism in 23-year old normal woman during and after cyclical treatment with Delpregnin

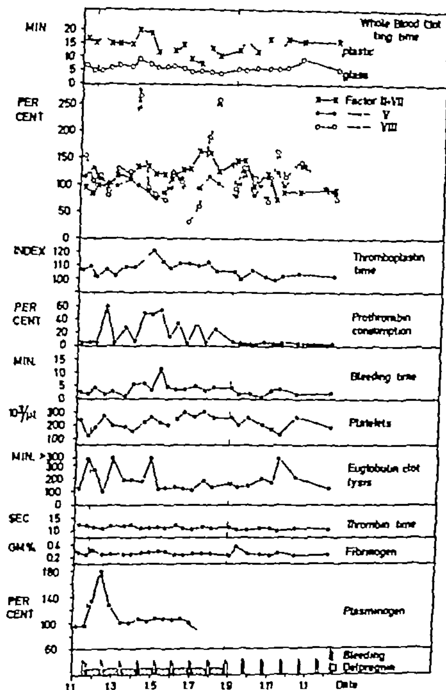


Fig. 1. Changes in the hæmostatic mechanism in a 33-year old normal woman during and after cyclical treatment with Delpregnin.

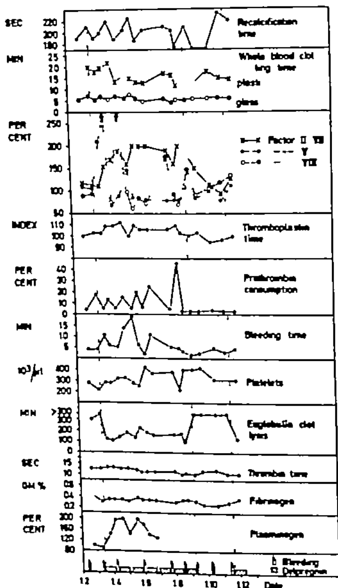


Fig Changes in the hemostatic mechanism in 23-year old normal woman during and after cyclical treatment with Delpregnin.

cycle immediately before the treatment was started Both during the treatment period and during the period following medication the same tests were performed twice a month (during menstruation and in the middle of the cycle) The observation period was 7 to 16 months and the treatment period 3 ½ to 14 months. All blood samples were taken between 8 a.m. and 10 a.m on ambulant non fasting patients

The second group consisted of 11 healthy women in their 5th to 7th month of pregnancy In order to obtain a comparable series of data from the pregnant women they were all examined once with the same tests as the first group of patients.

The tests performed are listed in Table I The blood sampling technique coagulation and fibrinolytic methods were the same as used in previous investigations (Amris 1966 Amris and Kjeldsen 1966) Plasma clot lysis with urokinase (UK) and streptokinase (SK) was determined in the following way 0.2 ml citrated plasma+0 2 ml of the fibrinolytic agent dissolved in Owren s buffer to desired concentration+0 2 ml thrombin solution (10 units per ml) were mixed simultaneously in a test tube placed in a water-bath at 37 C The time for complete lysis of the clot formed was recorded by means of a stop-watch.

Results

All 4 patients in the first group showed similar changes in the coagulation components during treatment with Delpregnin. Figures 1 and 2 show the changes in the different measurements in 2 of the 4 patients. Each parameter will be analysed briefly in details below

Coagulation tests

Whole blood clotting time A slight shortening was observed during the treatment. The clotting time returned to normal shortly after medication had been discontinued.

Prothrombin consumption. In all 4 patients the consumption of prothrombin had a tendency to decrease (increased consumption index) during the treatment. In 2 of the patients clearly abnormal

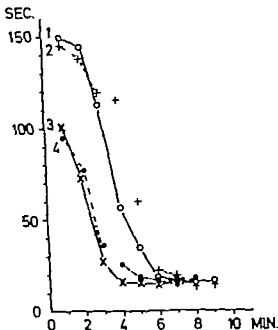


Fig. 3. Typical example of the accelerated thromboplastin screening test observed in patients during treatment with Delpregnin and demonstration of the activating effect of the patient plasma on thromboplastin generation in normal plasma. *Abscissa*: Incubation time in minutes. *Ordinate*: Substrate plasma clotting time in seconds. *Curves*: normal control 2. patient before treatment 3. patient during treatment 4. normal plasma+20 per cent of the patient' plasma.

values were observed on several occasions. The post-treatment values were normal in all patients.

Thrombin generation test. No significant changes in the speed of formation and in the yield of thrombin were observed.

Thromboplastin screening test. Characteristic of all 4 patients was acceleration and increase of thromboplastin formation as indicated by shortened initial and minimal clotting times. These changes occurred as early as the first treatment-cycle and lasted for the whole treatment period with only slight variations. The acceleration of thromboplastin formation ceased 1 to 2 months after the discontinuance of medication. The typical findings in

one of the patients are shown in Figure 3 The figure also shows that the thromboplastin formation in normal plasma is accelerated after addition of 20 per cent of the patient's plasma This may indicate the presence of a thromboplastic accelerator in the patient's blood.

Thromboplastin time After some weeks of treatment a temporary shortening was observed. In Figures 1 and 2 the shortening is indicated by an increase in the index $\frac{\text{normal control}}{\text{patient}} \times 100$

Changes in clotting factors

Factors II and VII (the p and p-test) A significant increase was seen in all 4 patients. This increase began soon after commencing treatment and reached a maximum after 4 to 6 weeks During the rest of the treatment period this high level was maintained. The values returned to normal during the first or second cycle after cessation of medication.

Factor V Except for a few peaks indicating moderately increased activity factor V did not show any characteristic changes during treatment.

Factor VIII During treatment the activity of factor VIII varied considerably from excessively high values (300–400 per cent) to moderately lowered values (40–60 per cent) The variations ceased after treatment had been discontinued, and could not be correlated with the other changes observed.

Fibrinogen and fibrinolytic moieties

Neither the *fibrinogen* concentration nor the plasma *thrombin time* showed any changes during treatment. The concentration of *plasminogen* was increased significantly during the first 2 to 4 cycles of treatment. Unfortunately some of the samples for plasminogen determinations were lost, and 3 of the patients were not followed systematically to the end of the study As is evident from Figures 1 and 2 however we found in all 4 patients a normal plasminogen concentration after 2 to 3 months of treatment and normal values were found during the rest of the treatment period

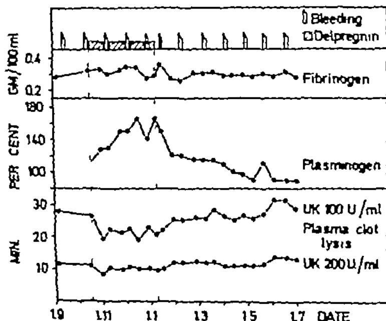


Fig. 4. Changes in plasminogen concentration and plasma clot lysis with urokinase in a 44-year old normal woman during and after cyclical treatment with Delpregnin.

The euglobulin clot lysis varied from patient to patient, and in the same patient from time to time. In 2 patients a definite shortening of the lysis time was observed during treatment. Excessive inhibition of fibrinolysis can be excluded, but the results do not permit any conclusions regarding possible minor variations in the fibrinolytic activity.

In order to reveal any possible development of fibrinolytic inhibition the lysis times of plasma clots with UK and SK were determined. Three concentrations of UK (400, 200 and 100 units per ml) and of SK (500, 250 and 125 units per ml) were used. Prolongation of the clot lysis time, indicating increased inhibition was not observed in any case. On the contrary a moderate shortening of the lysis times with UK was seen in all 4 patients during treatment. An example is given in Figure 4 from which it appears that the shortening of the lysis time ceases when the plasminogen concentration is normal.

Table II. *Some Coagulation Findings in 11 Healthy Women in the 5th to 7th month of Pregnancy The Values are Mean Values ± SD and the Numbers in Brackets Indicate the Range of Values Recorded*

Test	During Pregnancy	Normal Range
Whole blood clotting time plastic tubes (min)	15 ± 2.7 (11−19)	15−25
Factor VIII (per cent)	135 ± 100 (51−390)	60−160
Factor V (per cent)	136 ± 31 (100−200)	80−120
Factors II+VII (per cent) (Owren s p & p-test)	155 ± 21 (133−200)	80−120
Fibrinogen (g/100 ml)	0.37 ± 0 09 (0.21−0 53)	0.20−0.40
Plasminogen (per cent)	160 ± 13 (146−180)	20−120
Prothrombin consumption (per cent)	11 ± 7 (4−22)	0−30
Bleeding time (min.)	1½−4¼	≤5
Platelets ($10^3/\mu l$)	270 ± 57 (204−364)	150−400

Platelets and bleeding time

The *platelet counts* in 3 of the patients showed a slight increase but all counts were within the normal range In 3 patients the *bleeding time* was prolonged on one or more occasions This was most pronounced in the patient shown in Figure 2 She had a more or less prolonged bleeding time during the greater part of the treatment period. Platelet studies including platelet aggregation with ADP (adenosin-diphosphate) clot retraction and phase-contrast microscopy of platelet rich plasma were carried out in all patients who showed prolonged bleeding time but these studies did not reveal any platelet abnormalities The platelet thromboplastic function was also found to be normal as judged from the results of the thrombin generation tests. After cessation of medication the bleeding time was normal in all patients and none of them complained of an abnormal bleeding tendency or of easily acquired bruises.

Changes in coagulation during pregnancy

In Table II some of the measurements in the 11 healthy pregnant women are summarized. It appears that factors II and VII, plasminogen and to a slighter degree factor V were increased. Factor VIII showed a great variability. The whole blood clotting time was short, and in 10 out of the 11 women an acceleration of the thromboplastin generation was observed. The degree of activation was similar to that observed in patients treated with Delpregnin. In the majority of pregnant women the thrombin generation was high but still within normal limits. None of the patients showed a shortening of the euglobulin clot lysis time. The plasma thrombin time was also within normal limits.

Discussion

The present study shows that the changes in the coagulation mechanism observed during treatment with Delpregnin are similar to those seen during normal pregnancy with regard to an increase in prothrombin-proconvertin, thromboplastin formation, and plasminogen. The changes in the first two factors were observed during the whole treatment period while the plasminogen concentration returned to normal after 2 to 3 months of treatment. This might be due to a resistance to the ingested hormone or to an increased consumption caused by a speeded-up haemostatic turnover, *viz.* increased fibrin formation and simultaneous fibrinolysis keeping the haemostatic balance in equilibrium.

Increased concentrations of fibrinogen and factors V and VIII have been claimed to indicate a hypercoagulable state (Egeberg, 1964) possibly associated with a greater risk of thrombosis. An increase in factor VIII during short-term treatment with Enovid® was reported by Egeberg and Owren, 1963, and among others Brackman and Astrup 1964, Miller *et al.* 1965, and Donayre and Pincus 1965 found an increased fibrinogen concentration during treatment with different gestagens. We found no increase in fibrinogen or factor V and only temporary and varying changes in the activity of factor VIII. These varia-

Table II. *Some Coagulation Findings in 11 Healthy Women in the 5th to 7th month of Pregnancy The Values are Mean Values ± SD and the Numbers in Brackets Indicate the Range of Values Recorded*

Test	During Pregnancy	Normal Range
Whole blood clotting time plastic tubes (min.)	15 ± 2 7 (11—19)	15—25
Factor VIII (per cent)	135 ± 100 (51—390)	60—160
Factor V (per cent)	136 ± 31 (100—[illegible]00)	80—120
Factors II+VII (per cent) (Owren s p & p-test)	155 ± 21 (133—200)	80—120
Fibrinogen (g/100 ml)	0 37 ± 0 09 (0.21—0 53)	0.20—0.40
Plasminogen (per cent)	160 ± 13 (146—180)	70—120
Prothrombin consumption (per cent)	11 ± 7 (4—22)	0—30
Bleeding time (min.)	1½—4¼	≤5
Platelets ($10^3/\mu l$)	270 ± 57 (204—364)	150—400

Platelets and bleeding time

The *platelet counts* in 3 of the patients showed a slight increase but all counts were within the normal range In 3 patients the *bleeding time* was prolonged on one or more occasions. This was most pronounced in the patient shown in Figure 2 She had a more or less prolonged bleeding time during the greater part of the treatment period Platelet studies including platelet aggregation with ADP (adenosin-diphosphate) clot retraction and phase-contrast microscopy of platelet rich plasma were carried out in all patients who showed prolonged bleeding time but these studies did not reveal any platelet abnormalities The platelet thromboplastic function was also found to be normal as judged from the results of the thrombin generation tests. After cessation of medication the bleeding time was normal in all patients and none of them complained of an abnormal bleeding tendency or of easily acquired bruises.

Further conclusions regarding the mechanism of the changes and their physiological significance are not possible within the limits of our present knowledge of the synthesis of clotting components. The changes in the coagulability are of the same degree and direction as those observed during normal pregnancy. A connection between "hypercoagulability" and thrombosis has never been demonstrated, but cannot be ruled out altogether. On the basis of our present knowledge of these problems we therefore feel that previous thromboembolic episodes should be regarded as a contraindication to the administration of oral contraceptives. We do not feel, however, that the coagulation changes observed go against the use of Delpregnin and other oral contraceptives in normal healthy women.

SUMMARY

Extensive coagulation studies were carried out at short intervals in 4 women with normal menstrual function before, during, and after cyclical treatment with Delpregnin® (each tablet of Delpregnin contains 5 mg of megestrol acetate + 0.1 mg of mestranol). The observation period was 7 to 16 months, and the treatment period 3½ to 14 months.

During treatment the following changes were observed: Increase in factors II and VII (Owren's p and p-test), accelerated thromboplastin formation and increased concentration of plasminogen. The concentration of factor VIII varied from considerably raised values to moderately lowered values. No significant changes were seen in factor V, platelets, fibrinogen and fibrinolytic activity (euglobulin clot lysis). The changes began shortly after treatment had been started, reached a maximum during the course of treatment, but without any evidence of a cumulative effect. The values all returned to normal shortly after treatment had been discontinued. Changes of the same degree and direction were demonstrated in 11 healthy women in the 5th to 7th month of pregnancy. Plasma clot lysis experiments with urokinase and streptokinase showed that no inhibition of activator-induced clot lysis developed during the treatment.

The results are discussed, and it is concluded that on the basis

tions in our results might be due to interference with the action of an "unspecific" coagulation accelerator rather than to true changes in the concentration of this clotting factor The same variability was seen in the group of pregnant women The acceleration of thromboplastin formation invariably seen in all the patients can be observed in patients with active thrombotic dis ease *but certainly also in patients who never develop thrombotic* disorders *e g* during normal pregnancy as is demonstrated by the present results

The results of the clot lysis experiments with UK and SK revealed that no inhibition of the activator induced fibrinolysis developed during the treatment period. This is in accordance with the findings of Brackman and Astrup 1964 and in contrast to the increased inhibitor concentration reported to develop during normal pregnancy (Brackman and Astrup, 1963) *The shortened clot lysis time with UK corresponded to* the elevation in plasminogen and is probably a function of this increase An increased thrombotic risk caused by fibrinolytic inhibition seems unlikely

The cause of the prolonged bleeding time occasionally observed in the patients remains obscure No changes in the platelet func tion could be demonstrated The prothrombin consumption was decreased on one or more occasions in two of the patients. This might be due to a qualitative platelet defect. However we found *no correlation between the bleeding time prothrombin* consumption and the other changes observed. None of the patients had spontaneous bleeding or showed any tendency to bruises Among 270 patients on long term treatment with Delpregnin bleeding symptoms have never been observed (Starup unpublished data) The changes observed are probably of no *clinical significance* but will be the subject of further investigations

The present study shows that the hæmostatic changes during treatment with Delpregnin

1) begin immediately after the treatment has been started
2) increase to a maximum during the treatment without any evidence of a cumulative effect, and
3) disappear shortly after the treatment has been discontinued.

Sobrero *A. J* *Fenichel* R. L and *Singher H O* J Amer med. Ass. 185 36 963
Spittel *J A. Owen* C. A. *Thompson J H* and *Bowie W H. J* In Final report of Enovid by the Ad Hoc Committee for the evaluation of a possible etiologic relation with thromboembolic condition. September 963, p. 3
Wolf P J clin. Path. 6 34, 1953

Received on May 9th, 966

of our present knowledge the authors feel that previous thromboembolic episodes should be regarded as a contraindication to the use of oral contraceptives but we do not feel that the coagulation changes observed contraindicate the use of these drugs in normal, healthy women

REFERENCES

Amris C. J Scand. J Hæmat. *3* 19 1966
Amris C. J and *Kjeldsen* J., Acta obst. gynec. scandinav *45* 180 1966
Biggs R. and *Macfarlane* R. G "Human blood coagulation and its disorders Oxford: Blackwell Scientific Publications 1962
Brackman P and *Astrup* T Scand. J clin. Lab Invest. *15* 603 1963
Brackman P and *Astrup* T Lancet *II* 10 1964
Brehm H Int. J Fertil. 9 45 1964
Donayre J and *Pincus* G Metabolism *14* 418 1965
Egeberg O "Studies on human blood coagulation and hæmostasis Universitetsforlaget, Oslo 1964
Egeberg O and *Owren* P A Brit. med. J *1* 220 1963
Hicks N D and *Pitney* W R. Brit. J Hæmat. 3 ~~ 1957
Hougie C. *Rutherford* R. N *Banks* A. L. and *Coburn* W A Metabolism *14* 411 1965
Jacobsson K. Scand. J clin. Lab Invest Suppl *14* 1955
Jordan W M Lancet 2 1146 1961
Margulis R R. *Ambrus* J L *Mink* I B and *Stryker* J C Amer J Obstet. Gynec. *93* 161 1965
Mc Intyre N *Phillips* M J and *Voigt* J C Brit. med J 2 1079 1962
Miller S P *Lee* S L and *Ritz* N Metabolism *14* 398 1965
Minogue W F *Halperin* I C *Soler-Bechar* J *Varriale* P and *Flood* F B New Eng. J Med. 268 1037 1963
Nilsson I M. *Blombäck* M and *von Francken* I Acta med. scand *159* 35 1957
Nilsson I M. and *Olow* B Acta chir scand. *123* 247 1962
Ollendorff P Thrombos Diathes hæmorrh (Stuttg.) *4* 244 1960
Owren P A and *Aas* K Scand J clin. Lab Invest *3* 201 1951
Pillips L. L. *Turksoy* R. N and *Southam* A. L Amer J Obst. & Gynec *82* 1216 1961
Pilgeram L. O Brit. med. J *1* 883 1964
Powell L. C *Guest* M. M and *Bond* T P Amer J Obst. & Gynec *93* 167 1965
Rapaport S I Proc. Conf Thromboembolic Phenomena in Women G D Searle & Co (1962) appendix V p 154
Schatz I J *Smith* R. F *Breneman* G M and *Bower* G C J Amer med. Ass *188* 493 1964

contrast [colon by the method of Welin double-contrast cystography (Jensen and Holm 1965 Johannessen 1965)] and on the basis of Roland's (1963) experience of hysterography followed by insufflation of carbon dioxide in examining infertile women with tubal occlusion the following double-contrast method for hysterography was worked out.

Method

Hysterosalpingography was carried out within the first two weeks of the cycle using a Malmström apparatus with the patient tilted slightly into a Trendelenburg position on a couch fitted with TV equipment. By moderate distal traction on the Malmström apparatus, the device is seen on the TV screen straightened cranio-caudally as much as possible Moreover the transverse plane of the device should be as far as possible parallel with the couch. Then the contrast medium (Urografin® 76 % 0.5–2 ml) is injected, if possible in such a way that the contrast medium just reaches the uterine cornua Thereafter the cock of the Malmström apparatus is closed and the syringe with Urografin® is exchanged for a 50 ml glass syringe filled with carbon dioxide. With light pressure carbon dioxide is now injected until the uterine cavity is almost completely rinsed" of (positive) contrast medium, and at that moment (controlled on the TV screen) the exposure is made As a rule one exposure is sufficient.

Complications

The first patient developed transient, mild pain in the right shoulder The subsequent patients were tilted slightly into a Trendelenburg position and remained in this position for 15 minutes after the examination was completed. With this positioning, we have not had any complications apart from those which are common following hysterosalpingography such as mild, transient pelvic pain and slight bleeding from the portio vaginalis.

Fischer Rasmussen, W and Guttorm, E Acta obst. et gynec scandinav 46, 92, 1967

From the Department of Radiology (Professor Gregers Thomsen) and the Department of Obstetrics and Gynæcology A-I (Professor Dyre Trolle and Børge Sørensen M.D) the University Hospital Copenhagen Denmark.

DOUBLE CONTRAST HYSTEROSALPINGOGRAPHY FOR THE VISUALIZATION OF INTRAUTERINE CONTRACEPTIVE DEVICES

BY

W FISCHER RASMUSSEN AND E GUTTORM

When using intrauterine contraceptive devices it is often desirable to ascertain the position of the device after its insertion The object may be to ascertain possible relationships between the position of the device and side effects in the form of pain and/or metrorrhagia or it may be to gain an impression of how large a part of the uterine cavity is protected by the device with a view to the greatest possible contraceptive effect.

By the methods available at present, however these objectives can only be partially accomplished. Probing the uterine cavity [as with a Beolocator (Rosen 1965)] affords information only as to whether or not a device is present. Plain films show only whether or not the device is in the true pelvis With conventional hysterosalpingography the device is hidden by the injected contrast medium (Urografin®) Even when the medium was diluted to 20 % it was not possible in the present study to obtain a satisfactory difference in the intensity of contrast between the medium and the device

Burnhill and Birnberg (1965) have solved this problem by superimposing a plain film of the uterus with the device *in situ* over a film of the contrast filled uterus in a conventional exposure Apart from involving two exposures this method requires that exactly the same position be maintained during both.

On the basis of other X Ray diagnostic methods using double

contrast (colon by the method of Welin double-contrast cystography (Jensen and Holm, 1965 Johannesen 1965)] and on the basis of Roland s (1963) experience of hysterography followed by insufflation of carbon dioxide in examining infertile women with tubal occlusion the following double-contrast method for hysterography was worked out.

Method

Hysterosalpingography was carried out within the first two weeks of the cycle using a Malmström apparatus with the patient tilted slightly into a Trendelenburg position on a couch fitted with TV equipment. By moderate distal traction on the Malmström apparatus, the device is seen on the TV screen straightened craniocaudally as much as possible Moreover the transverse plane of the device should be as far as possible parallel with the couch. Then the contrast medium (Urografin® 76 % 0 5–2 ml) is injected, if possible in such a way that the contrast medium just reaches the uterine cornua. Thereafter the cock of the Malmström apparatus is closed and the syringe with Urografin® is exchanged for a 50 ml glass syringe filled with carbon dioxide With light pressure carbon dioxide is now injected until the uterine cavity is almost completely rinsed" of (positive) contrast medium, and at that moment (controlled on the TV screen) the exposure is made As a rule one exposure is sufficient.

Complications

The first patient developed transient, mild pain in the right shoulder The subsequent patients were tilted slightly into a Trendelenburg position and remained in this position for 15 minutes after the examination was completed. With this positioning, we have not had any complications apart from those which are common following hysterosalpingography such as mild, transient pelvic pain and slight bleeding from the portio vaginalis.



Fig 1 A normal uterus without a device

Material

The material comprises 27 women who had had a Birnberg bow No 5 inserted, twenty-one at 8–38 weeks (mean 14 weeks) *post partum* three more than one year *post partum* and three at 10–38 weeks (mean 22 weeks) after induced abortion On average the device had been *in situ* for almost eight weeks (4–16 weeks) prior to radiological examination The patients were selected at random

Results

Fig 1 illustrates the method on a normal uterus without a device The outlines of the uterine cavity are distinct Fig 2 shows a



Fig. 2. Uterine cavity in which the position of the contraceptive device (Birnberg bow) is presumed t be correct



Fig. 3. Device in partially intracervical position.

uterus with a Birnberg bow No. 5. The figure gives an impression of the position of the device in the cavity and at the same time it is possible to estimate how large a part of the uterine cavity is protected by the device. The position of this device must be considered suitable while in the case shown in Fig 3 the Birnberg bow is partially intracervical. In this case it had been impossible to detect the partial intracervical position of the device by probing In the whole series there were two cases showing a partially intracervical position. In one case moreover there was such a great distance from the fundus to the proximal part of the Birnberg bow that it was doubted whether it afforded sufficient contraceptive security In all, three Birnberg bows were re-inserted on the basis of the X-Ray findings in two cases the same size (No. 5) and in one case a smaller size (No 6)

Finally Fig 4 illustrates a case in which the distal part of the Birnberg bow shows a marked projection into the lower uterine segment (Burnhill and Birnberg's prong sign") On the basis of the present small series it is not possible to state whether this finding bears any relation to complaints of menstrual like pain or bleeding disturbances. In such cases it is reasonable to choose



Fig 1 A normal uterus without a device

Material

The material comprises 27 women who had had a Birnberg bow No 5 inserted twenty-one at 8–38 weeks (mean 14 weeks) *post partum* three more than one year *post partum* and three at 10–38 weeks (mean 22 weeks) after induced abortion On average the device had been *in situ* for almost eight weeks (4–16 weeks) prior to radiological examination The patients were selected at random

Results

Fig 1 illustrates the method on a normal uterus without a device The outlines of the uterine cavity are distinct Fig 2 shows a

By the method used it is impossible to decide whether absent tubal outflow is due to too little (positive) contrast medium, or whether it indicates a real obstruction to the passage through the Fallopian tube.

Conclusion

In the authors opinion the above hysterosalpingographic technique is an examination which can reasonably be offered to women with intrauterine contraceptive devices in cases where orientation concerning the situation of the device is wanted for some reason or other

To obtain experience relating to the radiological findings to clinical symptoms such as pain and metrorrhagia a larger number of patients must be examined.

Theoretically it is of interest to know whether the pregnancies which may occur in patients with intrauterine devices do happen in patients in whom X-rays have shown the smallest proportional protection of the uterine cavity by the device If this is so, as indicated by experimental investigations on animals (Carleton and Phelps 1933 Doyle and Margolis 1963) it may be considered whether radiological study of the relationship of the device to the uterine cavity should be performed as a routine on women in whom great contraceptive security is desired for important reasons (medical indications, previous Rhesus immunization, etc)

SUMMARY

Using Urografin® -6 and carbon dioxide the authors have worked out a double-contrast hysterosalpingography technique This method has proved well-suited for visualizing intrauterine contraceptive devices and thus may be of significance in demonstrating an extra corporal position of the device or incongruence between the device and the uterine cavity



Fig 4 Device with marked projection into the lower uterine segment (prong sign)



Fig 5 The mucosal relief in the uterus (secretory phase)

another model whose distal bow has a smaller transverse measurement.

The authors realize that the insufflation of carbon dioxide, performed with very moderate finger pressure but without pressure measurement, may have "blown" the uterus up to a larger volume than it naturally assumes around the device and that this may have resulted in an erroneous estimate of the size of the device in relation to the uterine cavity Since however we are dealing with a thick walled cavity and since double-contrast exposures of the uteri of a couple of patients without devices, compared with normal contrast exposures of the same patients, showed no difference in the size of the uterine cavity there does not seem to be any likelihood of such an increase in volume

An accidental finding, shown in Fig 5 was a pronounced mucosal relief of the endometrium in a patient whose first menstruation *post partum* occurred shortly after the examination Thus the film appears to give an impression of the endometrium in secretory phase

Lastly it should be mentioned that among the 27 patients we found absent tubal outflow on both sides in two and on one side in four patients.

Widholm, O and Ryynänen, V.A. Acta obst. et gynec. scandinav. 46, 147 1967

From the First and Second Women's Clinics (Professor A. Turunen and Professor P. Vara) Helsinki University Central Hospital Helsinki Finland

DIVERTICULUM OF THE FEMALE URETHRA

BY

O. WIDHOLM AND V.A. RYYNÄNEN

Diverticulum of the female urethra, although a relatively infrequent finding, in recent years has attracted increasing attention and the number of patients seeking treatment has risen rapidly. Disorders of the female urethra are seen sometimes by the gynaecologist and sometimes by the urologist, but because the urethra is located in "no man's land" neither of these special fields has given it much attention and abnormalities such as diverticula may pass unnoticed.

Ætiology

Most urethral diverticuli are noted among parous women aged between 25–50 years, a fact which suggests that it is an acquired condition. Congenital diverticuli have been seen in infants (Johnson 1938, McMahon, 1946, Parmenter 1941) but even in these cases inflammatory changes usually have been demonstrable in the glandular ducts of diverticular walls. It is probable that the infection originates in peri-urethral ducts situated like strands in the central and posterior parts of the urethra (Huffman, 1948, Tancer and Hyman, 1962). These glandular ducts are evidently highly susceptible to infection, friction and obstetric compression. The infected gland enlarges or breaks through and an abscess cavity forms in the potential urethrovaginal space. If the neck of the gland seals off an acute suburethral abscess occurs and may develop into a cyst, or if the

This investigation was supported by a grant from the Sigrid Juselius Foundation, Helsinki.

REFERENCES

Burnhill, M. S. and *Birnberg, C. H.*: Superimposition hysterography as a tool in the investigation of intrauterine contraceptive devices. Preliminary report. In: Intrauterine contraception. International Congress Series No. 86. Excerpta Medica Foundation 1965, p. 127–134.

Carleton, H. M. and *Phelps, H. J.*: J. Obst. & Gynaec. Brit. Emp. 40: 81, 1933.

Doyle, L. L. and *Margolis, A. J.*: Science 139, 833, 1963.

Jensen, J. and *Holm, H. H.*: Ugeskr. Læg. 127: 685, 1965.

Johannesen, S.: Danish med. Bull. 12: 193, 1965.

Roland, M.: Fertil. Steril. 14: 28, 1963.

Rosen, E.: Am. J. Obst. & Gynec. 93: 896, 1965.

Received on May 5th, 1966.

Widholm, O. and Rytkönen, V.A. Act. obst. et gynec. scandinav. 46, 107, 1967

From the First and Second Women's Clinics (Professor A. Turunen and Professor P. Vara) Helsinki University Central Hospital Helsinki Finland

DIVERTICULUM OF THE FEMALE URETHRA

BY

O. WIDHOLM AND V.A. RYTKÖNEN

Diverticulum of the female urethra although a relatively infrequent finding, in recent years has attracted increasing attention and the number of patients seeking treatment has risen rapidly Disorders of the female urethra are seen sometimes by the gynaecologist and sometimes by the urologist, but because the urethra is located in "no man's land" neither of these special fields has given it much attention and abnormalities such as diverticula may pass unnoticed.

Ætiology

Most urethral diverticuli are noted among parous women aged between 25–50 years, a fact which suggests that it is an acquired condition. Congenital diverticuli have been seen in infants (Johnson 1938 McMahon, 1946 Parmenter 1941) but even in these cases inflammatory changes usually have been demonstrable in the glandular ducts of diverticular walls. It is probable that the infection originates in peri-urethral ducts situated like strands in the central and posterior parts of the urethra (Huffman, 1948 Tancer and Hyman 1962) These glandular ducts are evidently highly susceptible to infection, friction and obstetric compression. The infected gland enlarges or breaks through and an abscess cavity forms in the potential urethrovaginal space If the neck of the gland seals off an acute suburethral abscess occurs and may develop into a cyst, or if the

This investigation was supported by a grant from the Sigrid Jusélius Foundation Helsinki.

abscess breaks through into the urethral canal there is a persistent channel or neck. Thus a so-called suburethral diverticulum results, and subsequently expands either as a result of fresh infections or the hydrostatic pressure via the urethra during micturition (Wharton and Kearns 1950 Dunn 1955) Also included in this group are the diverticuli arising from trauma in the musculature of the urethral wall produced by surgery childbirth, vaginal rupture or instrumentation of the urethra (Spraitz and Welch 1965)

Irrespective of the aetiology of the diverticulum the clinical picture is identical and the treatment the same usually operative.

Symptoms

All reports agree that symptoms of suburethral diverticuli may be present in varying degrees for many years prior to a definite diagnosis being established In all the reported series a complete range of symptoms referable to the lower urinary tract are noted. The patient herself or the doctor consulted has usually attributed the symptoms to cystitis. The difference is that the burning and pain in a patient with a diverticulum is of a different degree of severity from that generally seen in cystitis (Cook 1954) Micturition may be so painful that the patient dreads and tries to postpone it or facilitates it with thermotherapy and sitz baths. In many cases morphine injections have been required to relieve the severe pain In addition the pain radiates in severe form to the lower abdomen inguinal folds vagina and perineum (Counseller 1949) The symptoms may also include dysuria pyuria, haematuria etc Among the most important symptoms is dyspareunia (Cook and Pool 1949 Counseller 1949 Moore, 1952 Gilbert and Cintron 1954 Tancer and Hyman 1962) seen for example in 9 of the 11 patients Tancer and Hyman examined personally (*Hoffman and Adams* 1965 Spraitz and Welch 1965 Ferris 1965)

A suburethral mass was palpated in 21 of the 26 patients of Tancer and Hyman's series and in 19 cases purulent material flowed from the urethra when the mass was pressed. Urethroscopy is unreliable especially in cases where the lumen is very

small and in which the diverticulum may have been emptied previously

The common symptoms are disorders of micturition often urine goes on dripping after the bladder has been voided, since urine flows out of the diverticulum (Heaney 1949 Hoffman and Adams, 1965) Bloody or purulent discharge has also been noted in connection with urination, this being due to infection. Cultures have revealed in these cases both coliform bacteria and other gram-negative bacilli gram-positive cocci and sometimes even gonococci (Wharton and Kearns 1950 Gilbert and Cintron, 1954 Pinkerton 1956 Davies and Te Linde, 1958 Zinser 1954 Spraitz and Welch 1965) Often the patients have themselves noted a suburethral node, occasionally tender Such a node has frequently been confused with vaginal prolapse or cystocele (Cook, 1954)

Material

The first case was treated in the Women s Clinic by Prof A. Turunen in 1949 and subsequently the number of patients has increased steadily

The present series includes a total of 34 patients with urethral diverticulum treated in the First and Second Women s Clinics of Helsinki University Central Hospital in 1949–66 Efforts have been made to obtain accurate medical history data on the patients complaints and symptoms which owing to incomplete hospital records are in some cases, unfortunately somewhat indefinite

Table I shows that the majority of the cases were women of fertile age with a mean age of 41 years. Information on parity was available on 30 patients of whom 19 were parous. The diverticuli ranged in size from 2 to 4 cm in diameter and they were usually palpable Cystourethrography was carried out in 21 cases, and in 5 cases the X ray finding confirmed the diagnosis The treatment was operative in 27 cases and in 17 of them a pathological examination revealed definite inflammatory changes in the diverticular wall All the cases—apart from one fistula which was repaired—became symptom free immediately after the opera

abscess breaks through into the urethral canal there is a persistent channel or neck Thus a so-called suburethral diverticulum results and subsequently expands either as a result of fresh infections or the hydrostatic pressure via the urethra during micturition (Wharton and Kearns 1950 Dunn 1955) Also included in this group are the diverticuli arising from trauma in the musculature of the urethral wall produced by surgery childbirth, vaginal rupture or instrumentation of the urethra (*Spraitz and Welch*, 1965)

Irrespective of the ætiology of the diverticulum the clinical picture is identical and the treatment the same usually operative.

Symptoms

All reports agree that symptoms of suburethral diverticuli may be present in varying degrees for many years prior to a definite diagnosis being established. In all the reported series a complete range of symptoms referable to the lower urinary tract are noted. The patient herself or the doctor consulted has usually attributed the symptoms to cystitis. The difference is that the burning and pain in a patient with a diverticulum is of a different degree of severity from that generally seen in cystitis (Cook 1954) Micturition may be so painful that the patient dreads and tries to postpone it, or facilitates it with thermotherapy and sitz baths. In many cases morphine injections have been required to relieve the severe pain In addition the pain radiates in severe form to the lower abdomen inguinal folds vagina and perineum (Counseller 1949) The symptoms may also include dysuria pyuria hæmaturia etc Among the most important symptoms is dyspareunia (Cook and Pool 1949 Counseller 1949 Moore 1952 Gilbert and Cintron 1954 Tancer and Hyman 1962) seen for example in 9 of the 11 patients Tancer and Hyman examined personally (Hoffman and Adams 1965 Spraitz and Welch, 1965 Ferris 1965)

A suburethral mass was palpated in 21 of the 26 patients of Tancer and Hymans series and in 19 cases purulent material flowed from the urethra when the mass was pressed. Urethroscopy is unreliable especially in cases where the lumen is very

small and in which the diverticulum may have been emptied previously

The common symptoms are disorders of micturition often urine goes on dripping after the bladder has been voided, since urine flows out of the diverticulum (Heaney 1949 Hoffman and Adams 1965) Bloody or purulent discharge has also been noted in connection with urination, this being due to infection Cultures have revealed in these cases both coliform bacteria and other gram-negative bacilli, gram-positive cocci and sometimes even gonococci (Wharton and Kearns 1950 Gilbert and Cintron, 1954 Pinkerton 1956 Davies and Te Linde 1958 Zinser 1954 Spraitz and Welch 1965) Often the patients have themselves noted a suburethral node occasionally tender Such a node has frequently been confused with vaginal prolapse or cystocele (Cook, 1954)

Material

The first case was treated in the Women s Clinic by Prof A. Turunen in 1949 and subsequently the number of patients has increased steadily

The present series includes a total of 34 patients with urethral diverticulum treated in the First and Second Women s Clinics of Helsinki University Central Hospital in 1949–66 Efforts have been made to obtain accurate medical history data on the patients complaints and symptoms which owing to incomplete hospital records, are in some cases unfortunately somewhat indefinite

Table I shows that the majority of the cases were women of fertile age with a mean age of 41 years. Information on parity was available on 30 patients of whom 19 were parous The diverticuli ranged in size from 2 to 4 cm in diameter and they were usually palpable Cystourethrography was carried out in 21 cases, and in 15 cases the X ray finding confirmed the diagnosis. The treatment was operative in 27 cases, and in 17 of them a pathological examination revealed definite inflammatory changes in the diverticular wall. All the cases—apart from one fistula which was repa red—became symptom-free immediately after the opera

Table I

Case	Age	Parity	Urin. Pass.	Urin. Inf.	Size of the Divert.	X-ray Exam.	Operation	P.A.D.
1	40	—	+	+	2 cm	+	Conservative treatment	—
2	46	III	+	+	4 cm	—	Extirp. of divert.	Infl. changes
3	30	—	+	+	2 cm	Negat.	Conservative treatment	—
4	27	—	+	+	3 cm	+	Extirp. of divert.	—
5	39				2 cm	—	″ ″	No infection
6	33	II	—	—	2 cm	Negat.	″ ″	—
7	48		—	—	2 cm	—	″	—
8	39	II(III)	—	—	2 cm	Negat.	Conservative treatment	—
9	42	II(V)	—	—	2 cm	—	Extirp. of divert.	—
10	40	—	+	—	3 cm	—	″ ″	—
11	43	V(VIII)	—	+	3 cm	Negat.	″ ″	Chron. inf
12	34	I	+	—	3 cm	—		Infection
13	35	III(V)	—	—	3 cm	Negat.	″ ″	″
14	50	III	+	—	3 cm	Posit.	″ ″	″
15	48	—	+	—	2 cm	″	″ ″ ″	Chron. inf
16	46	O(I)	—	—	3 cm			—
17	40	—	—	—	3 cm	″	″ ″	Chron. inf
18	51	II(III)	+	+	3 cm	—		No clear inf
19	27	III(IV)	+	+	2 cm	Negat.	Conservative treatment	—
20	28				2 cm	—	Extirp. of divert.	No infection
21	44	II(III)	+	—	3 cm	Posit.	″ ″	Chron. inf
22	25	—	—	—	2 cm	Negat.	Conservative treatment	—
23	54	II	+	+	3 cm	Posit.	Extirp. of divert.	Chron. inf
24	61	—	—	—	2 cm	—	Conservative treatment	—
25	56		—	—	2 cm	—	Extirp. of divert.	Infection
26	28	—	+	+	4 cm	Posit.	″	″
27	44	VI(VII)	+	+	4 cm		″	No infection
28	52	I	—	+	2 cm	—		Infection
29	54	II	—	+	3 cm	Posit.	″ ″	Chron. inf
30	54	—(II)	+	+	2 cm		″	″
31	28	—	+	+	3 cm		″ ″	No infection
32	28	—	+	+	3 cm		Conservative treatment	—
33	38	I	+	+	3 cm	Negat.	Extirp. of divert.	Chron. inf
34	61	II	+	+	3 cm	Posit.	″	″

Table II

	Patients
Frequency burning, urgency	28
Dysuria (radiation to lower abdomen, vagina perineum and inguinal folds)	17
Urinary tract infection	20
Dyspareunia	1
Incontinence	1
Purulent flow following micturition	9
Dripping of urine after micturition	8
Chills and fever with urinary complaints	7
Patient felt a node at the orifice of external genitals	3
Blood seen during or after micturition	3
Complete retention of urine	

tion. In 7 cases not subjected to operation treatment was either by urethral dilatation and antibacterial agents or by antibiotics alone.

Since detailed information was not available on all the patients the most important symptoms are listed in Table II

As might be expected, urinary complaints are prominent, but they differ from the commonly found pyelocystitis in that the pain and suffering is more intense It is natural that urinary tract infections are frequent, as the walls of the diverticulum are usually inflamed. Urinary incontinence is an important symptom. The dripping of urine after micturition however is probably due to the voiding of the diverticulum. Dyspareunia and a palpable mass are also among the characteristic symptoms.

Discussion

The patients ages in the series of Tancer and Hyman (1962) ranged from 29 to 65 years which agrees well with the present series. In Spraitz and Welch s (1965) series the mean age was 46 years. Davies and Te Linde (1958) agree that there is no relationship to parity and find the lesion to be rare in the grand multipara. Spraitz and Welch (1965) report that 39 per cent of their series were nulliparous

In general, the present patients had long suffered from their

Table I

Case	Age	Parity	Urin. Pain	Urin. Inf	Size of the Divert.	X-ray Exam	Operation	P.A.D.
1	40	–	+	+	2 cm	+	Conservative treatment	–
2	46	III	+	+	4 cm	–	Extirp. of divert.	Infl changes
3	30	–	+	+	2 cm	Negat.	Conservative treatment	–
4	27	–	+	+	3 cm	+	Extirp. of divert.	–
5	39				2 cm	–	〃 〃	No infection
6	33	II	–	–	2 cm	Negat.	〃	–
7	48		–	–	2 cm	–	〃	–
8	39	II(III)	–	–	2 cm	Negat.	Conservative treatment	–
9	42	II(V)	–	–	2 cm	–	Extirp of divert.	–
10	40	–	+	–	3 cm	–	〃	–
11	43	V(VIII)	–	+	3 cm	Negat.	〃	Chron. inf
12	34	I	+	–	3 cm	–		Infection
13	35	III(V)	–	–	3 cm	Negat.	〃	〃
14	50	III	+	–	3 cm	Posit.	〃	〃
15	48	–	+	–	2 cm	〃	〃	Chron. inf
16	46	O(I)	–	–	3 cm	〃	〃	–
17	40	–	–	–	3 cm		〃 〃	Chron. inf
18	51	II(III)	+	+	3 cm	–	〃	No clear inf
19	27	III(IV)	+	+	2 cm	Negat.	Conservative treatment	–
20	28				2 cm	–	Extirp of divert.	No infection
21	44	II(III)	+	–	3 cm	Posit.	〃 〃	Chron. inf
22	25	–	–	–	2 cm	Negat.	Conservative treatment	–
23	54	II	+	+	3 cm	Posit.	Extirp. of divert.	Chron. inf
24	61	–	–	–	2 cm	–	Conservative treatment	–
25	56		–	–	2 cm	–	Extirp. of divert.	Infection
26	28	–	+	+	4 cm	Posit.	〃 〃 〃	〃
27	44	VI(VII)	+	+	4 cm		〃 〃	No infection
28	52	I	–	+	2 cm	–	〃 〃	Infection
29	54	II	–	+	3 cm	Posit	〃 〃	Chron. inf
30	54	–(II)	+	+	2 cm	〃	〃 〃	〃 〃
31	28	–	+	+	3 cm		〃 〃 〃	No infection
32	28	–	+	+	3 cm		Conservative treatment	–
33	38	I	+	+	3 cm	Negat.	Extirp of divert.	Chron. inf
34	61	II	+	+	3 cm	Posit.		〃

Table II

	Patients
Frequency burning, urgency	28
Dysuria (radiation to lower abdomen, vagina, perineum and inguinal folds)	17
Urinary tract infection	20
Dyspareunia	11
Incontinence	1
Purulent flow following micturition	9
Dripping of urine after micturition	8
Chills and fever with urinary complaints	7
Patient felt a node at the orifice of external genitals	5
Blood seen during or after micturition	3
Complete retention of urine	2

tion. In 7 cases not subjected to operation treatment was either by urethral dilatation and antibacterial agents or by antibiotics alone.

Since detailed information was not available on all the patients the most important symptoms are listed in Table II

As might be expected, urinary complaints are prominent, but they differ from the commonly found pyelocystitis in that the pain and suffering is more intense It is natural that urinary tract infections are frequent, as the walls of the diverticulum are usually inflamed. *Urinary incontinence* is an important symptom. The dripping of urine after micturition, however is probably due to the voiding of the diverticulum. Dyspareunia and a palpable mass are also among the characteristic symptoms.

Discussion

The patients ages in the series of Tancer and Hyman (1962) ranged from 29 to 65 years which agrees well with the present series In Spraitz and Welch's (1965) series the mean age was 46 years. Davies and Te Linde (1958) agree that there is no relationship to parity and find the lesion to be rare in the grand multipara. Spraitz and Welch (1965) report that 39 per cent of their series were nulliparous.

In general, the present patients had long suffered from their

troubles and they had mostly been treated for cystitis or urethritis A striking feature however is that the pain is usually exquisitely severe in these cases (Cook, 1954) A common type of pain is dyspareunia reported in 11 cases in the present series but since we could not ourselves ask the patients about their complaints it is probable that the real incidence was higher

Urinary incontinence was present in 10 cases. It obviously results from the fact that the oedema surrounding the diverticulum and the outward pressure produced by the diverticulum itself disturb the function of the inner urethral meatus and stiffen the urethral walls.

Another similar symptom in 8 cases was the dripping of urine after the bladder had been voided as the contents of the diverticulum emptied. Heaney (1949) and Hoffman and Adams (1965) consider this an almost pathognomonic symptom. Purulent discharge during or after micturition often concomitant with sporadic fever are common symptoms and also fairly distinctive Two of the present patients showed complete retention of urine which had occurred on 4 occasions in one of the patients, as a result of severe inflammation of the diverticulum.

If the medical history is carefully recorded with the possibility of a diverticulum in mind, a suburethral mass can usually be found by palpation and inspection in the anterior vaginal wall As a rule the diverticulum is tender to palpation and often when pressed pus can be milked from the urethra In all the present cases the diverticulum was palpable and in 14 cases discharge occurred on pressure Bacterial cultures were not made in all the cases but in those that were made the most common finding was *Escherichia coli*, correlating well with the earlier reports. In 4 patients the diverticulum contained numerous calculi their incidence has previously been reported at 10–17 per cent (Herman and Greene 1944)

The diverticulum was demonstrated in 15 of the 21 patients examined by cystourethrography The contrast medium used was Mixobar (Astra) The tendency was to use pressure as a catheter similar to that used by *e g* Tancer and Hyman (1962) was not available In cases where infection had not blocked the lumen radiography was very helpful and illustrated the finding clearly



Fig.

Evacuation of the diverticulum by compression before radiography has been recommended, following which the contrast medium, as finely granular as possible should be introduced by excess pressure into the urethral region Taylor s modified pressure tube made from a Foley catheter has also been used for the purpose (Gilbert and Cintron, 1954 Stenström 1953) The value of radiography is reduced by the fact that the previous diagnosis is often obvious without it, and in addition it often fails to reveal an existing diverticulum (Counseller 1949)

Urethroscopy was performed in only 14 cases the lumen was readily visible in all of them, especially when the diverticulum was compressed at the same time In 2 cases there were 2 ostia in the same diverticular formation. An isthmus about 1 cm wide separated the ostia. In one of the cases a calculus was seen in the cavity through the ostium, and in this case urethroscopy was of great help in the operation. Without a urethroscope with 120–



Fig 2. *No* 23741 Inflammatory cell infiltration, haemorrhage and oedema in the stroma of urethral mucosa. The surface is partly necrotic and without epithelium partly coated by ordinary transitional epithelium. The finding suggests a chronic or subchronic inflammatory process. (C. v Numers)

130 forward-directed optical system and continuous lavage it is extremely difficult to examine the urethra adequately

In differential diagnosis urethral abscesses retention cysts of Skene s glands and tumours of the urethra such as carcinoma and myoma should be considered Chronic urethritis may also sometimes cause confusion

In all the cases where operation was possible the diverticulum was exstirpated. Conservative treatment with antibiotics and dilatation of the urethra were employed in only 7 cases and then either due to the patient s poor general condition or her refusal to submit to operation. The method of operation was identical in all the cases Preoperatively a Foley catheter was introduced into the bladder to facilitate localization and to visualize the lumen once the diverticular sac was opened. The diverticulum was excised from its surroundings via a longitudinal incision The diverticulum was resected about 2 mm above the ostium The ostium was closed transversely with atraumatic chromic catgut



Fig 3 N 37126 Pronounced chronic inflammation; over extensive areas the surface of the mucosa is necrotized and without epithelium The structure of the epithelium is normal, transitional (C Numers)

knotted sutures and covered by 2 layers and finally by mucous membrane Kirby (1949) warns against traumatization of the sphincter and should the excision fail Ellik (1957) recommends cleansing of the sac and packing with oxidized cellulose and closure of the vaginal wound. A catheter was usually left in place for 1–15 days a period during which the patient was given a course of sulphonamides or antibiotics following sensitivity tests It was sometimes difficult to close the diverticular ostium since infection had made the tissues fragile Ingelman-Sundb rg (1949) used the bulbocavernosus muscles as reinforcement. It is of the utmost importance to take good care of the urethral muscles and see to it that no granulation tissue remains in the sutured surfaces, although there must be no excessive tension. In one case a fistula developed as a result of severe infection, and excessive tension of the sutured surfaces this was, however easily corrected 2 months later Marked inflammatory changes



Fig 4 No. 37626 The highly inflamed superficial layers of urethral mucosa are necrotic almost throughout, partly covered by fibrinous detritus. There are minute remains of transitional epithelium heavily altered by the inflammation. A chronic, long-standing inflammation. (C v Numers)

were seen in 17 out of the 21 operation specimens examined 9 were chronic infections which had partly destroyed the diverticular walls In Figs. 2 3 and 4 examples are given of the inflammatory changes

The last 8 patients treated were operated on in the ventrolithotomy position (Widholm) This position facilitates surgery but produces difficulties for the anæsthetist and because of anæsthetic difficulties is not suitable for obese patients

SUMMARY

The ætiologic pathologic and clinical features of diverticulum of the female urethra are presented together with the findings in 34 patients treated in the First and Second Women's Clinics University of Helsinki during the period from 1949 to 1966 The ages of the patients ranged from 27 to 61 years The majority of

them were parous. Cystourethrographies were performed in 21 cases, and the diverticulum could be diagnosed in 15 of them. In 14 cases the diverticulum was visualized by urethroscopy The most common symptoms were frequent micturition, burning during or after micturition, pain urinary tract infections and dyspareunia 17 of the 21 specimens taken at operation showed distinct inflammatory changes in the diverticular walls in 9 of them the infection was chronic and had produced an almost complete necrosis of the diverticular wall. Surgery was carried out in 27 cases and in the last 8 cases the operation was performed in the lithotomy position.

REFERENCES

Appelgren A. Duodecim (Helsinki) 55 633, 939
Cook E. N Surg. Gynec. Obstet 99, 273 954
Counseller V S Amer J Obstet. Gynec. 57 31 949
Dunn R D West. J Surg. 63 696 953
Ferris, J H N Brit. med. J 2 738 1965
Gilbert C. R. A and *Cintron F J R.* Amer J Obstet. Gynec. 67 6 6 954
Henry N S. Amer J Obstet Gynec. 57 236 949
Herbut P A Urological Pathology Kimpton, London, 952 Vol. I
Herman L and *Greene L B.* J Urol. (Baltimore) 52 590 944
Hoffman M. J and *Adams W E* Amer J Obstet. Gynec. 92, 06 1965
Huffman J W Amer J Obstet Gynec. 55, 86 948
Ingelman-Sundberg, A. Nord. Med 42 168 949
Johnson C M J Urol (Baltimore) 39, 506 938
Latzko W and *Schiffmann J* Erkrankungen des weiblichen Harnapparates und ihre Beziehungen zu den weiblichen Generationsorganen. In: Biologie und Pathologie des Weibes ed. J Halban & L. Seitz, Band V/4 3. Urban & Schwarzenberg, Berlin & Wien, 928
McMahon S J Urol (Baltimore) 55 69, 946
Pinkerton J H M J Obstet Gynaec Brit. Emp 63, 76 956
Spraitz A F and *Welch J S* Amer J Obstet. Gynec. 9 0 3, 965
Stenstrom R Finska Lak. Sällsk. Handl. 96 62, 953
Tancer M L and *Hyman R* Amer J Obstet Gynec 84, 833, 962
Turunen A Personal communication
Wharton L. R. and *Kearns W* J Urol (Baltimore) 63 063, 959
Zinser H -K Die urologischen Erkrankungen der Frau In. Biologie und Pathologie des Weibes ed L. Seitz & A. I. Amreich, Band X, S 540. Urban & Schwarzenberg, Berlin 954 (S 696)

Received on May 3 st, 966

Borglin, N. E. and Heukensköld, F. Acta obst. et gynec. scandinav. 46, 119, 1967
From the Departments of Obstetrics and Gynaecology (Professor Stig Kullander) and of Surgery (Professor Helge Wulff) Malmö Allmänna sjukhus, Malmö Sweden

STUDIES ON SERUM COPPER IN PREGNANCY

BY

N. E. BORGLIN AND F. HEUKENSKJÖLD

Several investigations have demonstrated that serum copper increases during pregnancy (*Krebs* 1928 *Neuweiler* 1943 *Nielsen* 1944 *Holmberg* and *Laurell*, 1951 *De Vries* 1953) This increase has been ascribed to an increased production of hormones particularly of the oestrogenic hormones produced by the placenta. This assumption has been strengthened by the observation that administration of oestrogen to non-pregnant women produces an increase in the serum copper content (*Turpin et al.* 1950 *Elsner* and *Hornykiewicz* 1954 *von Studnitz* and *Berezin* 1958 *Russ* and *Raymunt* 1956 *Humoller et al.* 1960)

In a previous investigation (*Heikenskjöld* and *Hedenstedt* 1962) it was found that the serum copper concentration is lower during pregnancy terminating in spontaneous abortion than in normal pregnancy or cases of threatened abortion with a subsequently favourable course Therefore it was assumed that knowledge of the serum copper level might be of prognostic value in patients with threatened abortion. The series studied was however relatively small and allowed no definite conclusions as to the value of serum copper determination in threatened abortion

It was suggested that the decrease in the copper content in certain cases of spontaneous abortion might be due to insufficient oestrogen production. It is known that in the event of foetal death the concentration of oestrogen in the urine falls rapidly (Cassmer 1959) and that determination of oestrogen in the urine

Table I. *Serum Copper Values (μg/100 ml Serum) During Pregnancy in 162 Women*

Month	N	Range	M ± S.E.M.
III	25	133–237	172 ± 6.2
IV	28	128–286	187 ± 8.6
V	31	138–278	219 ± 6.3
VI	37	160–314	222 ± 5.9
VII	18	168–279	236 ± 6.4
VIII	14	189–459	242 ± 18.4
IX	9	224–345	273 ± 14.6

Table II. Serum Copper Values (μg/100 ml Serum) in 43 Women with *Threatened Abortion Grouped According to the Outcome*

Month	III		IV	
Outcome	Abortion	Continued Pregnancy	Abortion	Continued Pregnancy
	106	88	85	123
	116	107	102	125
	123	114	103	137
	125	146	115	142
	132	172	117	158
	133	173	121	190
	149		125	
	156		126	
	158		140	
	162		141	
	168		144	
	187		144	
	203		163	
	212		168	
			170	
			195	
			212	
N	14	6	17	6
Mean value ± S.E.M.	152 ± 7.9	133 ± 13.0	139 ± 8.1	146 ± 9.2

in threatened abortion may be of prognostic value (*Hähnel* and *Martin* 1964) Such determinations are however more expensive and more time-consuming than determination of the serum copper The purpose of the present investigation was to study in a large series the serum copper level during normal pregnancy and in threatened abortion In order to obtain further information that might be useful in the investigation of a possible relation between the serum copper content and the excretion of oestrogen in the urine the series was extended to include cases of legal abortion

Methods and Material

Blood samples for determination of the serum copper content were collected from a cubital vein of fasting patients between 7 and 9 a.m. The analyzes were made at the central laboratory of the hospital The excretion of oestrogens in the urine per 24 hours was determined by the method of *Brown* (1955) The clinical series consisted of 162 women with normal pregnancies 43 women with threatened abortion and 25 women undergoing legal abortion in the 14th to 20th week of pregnancy In the latter group the serum copper and the urinary excretion of oestrogens were determined before and after the termination of the pregnancy The legal abortions were done by hysterotomy In some of the cases the operation was extended to include sterilisation by tubal resection. In none of the cases was the postoperative course complicated.

Results

Serum Copper During Normal Pregnancy

The serum copper content was determined in 162 women in the 3rd to 9th month of pregnancy The results (Table I) showed a continuous linear increase from, on the average 173 microg Cu per 100 ml serum in the 3rd month to 273 microg Cu per 100 ml serum in the 9th month.

Serum Copper in Threatened Abortion

The group with threatened abortion (bleeding pain) consisted of 43 women 31 aborted and 12 went on to term. All of these

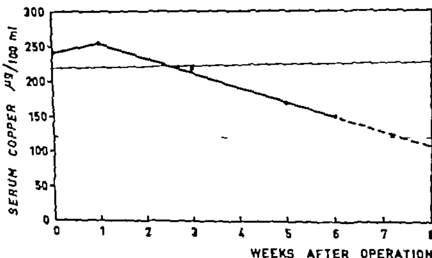


Fig. 1 Serum copper level in cases of legal abortion during the first 6 weeks after the operation.

—— approximate level of serum copper in normal pregnancy at this stage. median level of serum copper in non-pregnant women (120 microg Cu/100 ml serum).

are in good agreement with those stated in the literature (*Nielsen* 1944 *von Studnitz* and *Berezin* 1958 *De Jorge et al* 1965) Our results are in good agreement with those of *von Studnitz* and *Berezin* who used the same method for determination of the copper and found a moderate increase in the copper values (about 60 ~) from the 3rd to the 9th month of pregnancy The serum copper content and its increase varied widely from one individual to another and did not seem to be proportional to the increase in the production of oestrogen or of other hormones during pregnancy

Wide individual variations in the amount of serum copper were also found in the group of patients with threatened abortion (Table II) Irrespective of the outcome such patients showed on average lower values for serum copper than in the group of patients with normal pregnancies though the differences were not significant. Neither were any significant differences found be-

Table III *Serum Copper Values and Oestrogen Excretion Following Legal Abortion*

	Before Operation	Days after Operation		
		1	3	5
Serum copper (μg/100 ml serum)				
Mean-value	240	231	250	251
N	23	23	21	16
Oestrogen excretion (μg per 24 hours)				
Mean value	2503	576	396	96
N	25	24	22	21

women were 3–4 months pregnant. The results of the determination of the serum copper content in these patients are given in Table II

Serum Copper and Oestrogen Excretion in the Urine before and after Legal Abortion

The serum copper content and the excretion of oestrogen in the urine were determined before the operation and on the 1st, 3rd and 5th day after the operation and then at longer intervals up to 6 weeks after the operation. The results of these analyzes before and the first few days after the operation are given in Table III and the results of the copper determinations during the subsequent period in Fig 1

Table III gives the excretion of oestrogens as total oestrogen *i e* the sum of the fractions oestriol, oestrone and oestradiol-17 beta. The individual fractions however showed the same rapidly decreasing values.

Discussion

The increase in the serum copper content during normal pregnancy (Table I) was linear from the 3rd to the 9th month of pregnancy Our mean values for the various months of pregnancy

2. Neither threatened abortion nor abortion had any significant effect on the elevated serum copper content during preg nancy
3. No correlation was found between the decrease in the serum copper content and the excretion of oestrogen after legal abortion The oestrogen level diminished rapidly to the level normal for non-pregnant women, while the serum copper content was still increased 6 weeks after abortion
4. Determination of the serum copper content is of no prognostic value in threatened abortion.
5. Judging from our results it is also doubtful whether the serum copper level varies significantly with the hormonal phases of the normal menstrual cycle.

REFERENCES

Brown J B. Biochem. J 60 185 1955

Casmer O Acta endocrinol. 32, suppl. 45 1959

De Jorge F B Delascio D and Antunes M. L., Obstetrics & Gynecology 26 225, 1965

De Vries S. I Ned. Tijdschr Verlosk. 53 137 1953

Elsner P and Hornykiewicz, O Arch. Gynäk. 185 251 1954

Heijkenskjöld, F and Hedenstedt S., Acta obst. et gynec. scandinav 41 41 1962

Holmberg, C. G and Laurell C.-B. Scand. J Clin. Lab. Invest. 3 103 1951

Hunsaller F L, Mockler M. P Hollhaus J M., and Mehler D J J Lab. Clin Med. 56 222, 1960

Halmel R and Martin J D J Obst. Gyn Brit. Cwlth 71 599 1964

Krebs H A Klin. Wchnschr 7 584 1928

Lahey M E Gubler C J Cartwright G. E., and Wintrobe M. M. J Clin. Invest. 32 329 1953

Neuweiler W Helvet. med. acta 10 619 1943

Nielsen, L A. Acta med. scandinav 118 92, 1944

Roy E. J and Mackay R., J Obst. Gyn. Brit. Cwlth. 69 13, 1962

Roy E. J and Harkness R. A., J. Obst. Gyn. Brit. Cwlth. 70 597 1963

Russ, E M and Raymunt J Proc. Soc. Exper Biol. & Med. 92 465 1956

Sanai U Japan. J. Med Sci. Trans II Biochem. 3 1, 1934

Sepichneider P Ztschr f Geburtsh. 130 142, 1949

Turpin, R., Schmitt Jubeau, H and Jerome H Compt rend. Soc de biol. 144 352, 1950

von Studnitz W and Berezin D Acta endocrinol. 27 245 1958

Received on May 21st, 1966

tween the women who aborted and those who had threatened abortion with a favourable subsequent course

If the serum copper level were to decrease rapidly after a legal abortion it would perhaps suggest a prognostic value in cases of threatened abortion However it decreased only slowly and even 6 weeks after abortion it had not reached the normal level for non pregnant women Such a slow return of the serum copper level to normal has also been noted after delivery (*Nielsen*, 1944)

Since administration of oestrogen to non pregnant women causes an increase in the serum copper content it has been thought that the increase during pregnancy was due to an increased production of oestrogen But the increase in the copper content is not proportional to the marked increase in the production and excretion of oestrogens in the urine nor does the serum level of copper after legal abortion or after delivery decrease in proportion to the rapidly diminishing excretion of oestrogens (Table III and Fig 1) It is known that the excretion of oestrogen decreases rapidly after legal abortion and after foetal death (*Cassmer* 1959) A similar decrease has been observed in the blood oestrogen (*Roy* and *Mackay* 1962 *Roy* and *Harkness* 1963) Before legal abortion the total 24 hour excretion of oestrogens (oestriol oestrone and oestradiol-17 beta) was on the average 2.5 mg The day after the operation it was on the average 0 6 mg and 5 days after the operation it was less than 0 1 mg There was thus no parallel between the decrease of the serum copper content and the urinary excretion of oestrogen.

Sarata (1934) like *von Studnitz* and *Berezin* (1958) reported a variation of the serum copper level during normal menstrual cycle with an increase in the premenstrual phase Such variations have however been denied by several authors (*Nielsen* 1944 *Segschneider* 1949 *Lahey et al* 1953) and judging from our results such a cyclical variation appears unlikely The serum copper concentration does not react rapidly to variations in hormone production.

SUMMARY

1 The serum copper gradually increased from the 3rd to the 9th month of pregnancy

2. Neither threatened abortion nor abortion had any significant effect on the elevated serum copper content during pregnancy
3. No correlation was found between the decrease in the serum copper content and the excretion of oestrogen after legal abortion. The oestrogen level diminished rapidly to the level normal for non-pregnant women, while the serum copper content was still increased 6 weeks after abortion
4. Determination of the serum copper content is of no prognostic value in threatened abortion.
5. Judging from our results it is also doubtful whether the serum copper level varies significantly with the hormonal phases of the normal menstrual cycle

REFERENCES

Brown J B., Biochem. J. 60 185 1955

Cassmer O Acta endocrinol. 32 suppl. 45 1959

De Jonge F B Delascio D and *Antunes M. L.*, Obstetrics & Gynecology 26 225 1965

De Vries, S. I Ned. Tijdschr Verlosk. 53 137 1953

Elmer P and *Horstykiewicz, O.*, Arch. Gynäk. 185 251 1954

Heijkenskjöld, F and *Hedenstedt S.*, Acta obst. et gynec. scandinav 41 41 1962

Holmberg, C G and *Laurell, C.-B.*, Scand. J. Clin. Lab. Invest. 3 103, 1951

Hunsmoller F L., Mockler M. P Holthaus J M., and *Mehler D J* J Lab. Clin. Med. 56 222, 1960

Hehmel R., and *Martin J D* J Obst. Gyn. Brit. Cwlth 71 599 1964

Krebs, H A., Klin. Wchnschr 7 584 1928

Lahey M. E., Gubler C. J Cartwright G. E., and *Wintrobe M M.*, J Clin. Invest. 32 329 1953

Neuweiler W Helvet. med. acta 10 619 1943

Nielsen, L. A. Acta med. scandinav 118 92, 1944

Roy E. J and *Mackay R.*, J Obst. Gyn. Brit. Cwlth. 69 13, 1962

Roy E. J and *Harkness R. A* J Obst. Gyn. Brit. Cwlth. 70 597 1963

Russ, E M and *Raymunt J* Proc. Soc. Exper Biol. & Med. 92 465 1956

Sarata, U Japan. J Med. Sci. Trans. II Biochem. 3 1 1934

Sergschwilder P Zschr f Geburtsh. 130 142, 1949

Turpin, R., Schmitt Jubeau, H and *Jerome H* Compt. rend. Soc de biol. 144 332, 1950

von Studnitz W and *Berezin D* Acta endocrinol. 27 245 1958

Received on May 21st, 1966

Ganrot, P O and Bjerre B Acta obst. et gynec. scandinav 46, 126, 1967

From the Department of Clinical Chemistry (C.-B Laurell MD) and the Department of Obstetrics and Gynaecology (Professor S Kullander) Malmö General Hospital Malmö Sweden

α_1 ANTITRYPSIN AND α_2 MACROGLOBULIN CONCENTRATION IN SERUM DURING PREGNANCY

BY

P O GANROT AND B. BJERRE

Human serum contains at least three protease inhibitors (Heide *et al* 1965 Mehl *et al.* 1966 Ganrot, 1966a) The two whose properties are best known α_1 antitrypsin (α_1-AT) (Schultze *et al*, 1962) and α_2-macroglobulin (α_2-M) (Schönenberger *et al* 1958) are the main components of the electrophoretic α_1 and α_2-fractions of the serum. The normal concentration of α_1-AT in adults is said to be about 290 mg/100 ml (Schultze *et al.*, 1963) that of α_2-M about 200 mg/100 ml (Schultze *et al* 1963 Ganrot and Schersten 1967) The third inhibitor, which was called the conventional α_2-antitrypsin (Ganrot, 1966a) and which differs from α_2-M by its thermostability is probably identical with the so-called inter-α trypsin inhibitor (Heide *et al* 1965)

α_1-AT is one of the acute phase reactants (Kelley 1952) that increase in concentration in response to acute tissue damage and inflammation (Shulman 1952) while α_2-M in man remains practically unchanged in the presence of such conditions (Schumacher and Schlumberger 1963 Lundh, 1965) The concentration of α_2-M is much higher in children than in adults (Koch *et al* 1959 Hitzig, 1961 Weiss 1965) The adult level is not reached until the age of 25–30 years (Ganrot and Schersten, 1967) The concentration of α_2-M also varies with sex it is about 20 % higher in females than in males (Ganrot

and Scherstén, 1967) α_1-AT has not been found to vary with age or sex (Laurell and Ganrot, 1966) but a hereditary deficiency with about half of the normal serum concentration in heterozygotic carriers and only 5 20% of the normal concentration in homozygotes for the gene for the deficiency has been described (Laurell and Eriksson, 1963 Eriksson 1964 Laurell and Eriksson, 1965) The concentration of α_2-M in the serum has been reported to increase markedly during pregnancy (Schlagetter and Schwick, 1961 Schumacher and Schlumberger 1963) But the series hitherto reported have been small and the age and sex distribution of the subjects has not been considered in comparison with the normal series reported. The variation of α_1-AT during pregnancy has apperently not been studied by a specific technique. Of other acute phase reactants haptoglobin, for example, remains largely unchanged during pregnancy (Schumacher and Schlumberger 1963) while ceruloplasmin increases markedly (Krebs 1928 Holmberg and Laurell 1951)

This paper is concerned with an investigation of the effect of pregnancy on the concentration of the α_2-M in the serum, with due consideration of the normal variation with sex and age and its effect on the concentration of the serum α_1-AT

Clinical Materials

The investigation was carried out on 272 sera from 194 pregnant and 78 puerperal women. Samples collected during pregnancy were obtained at routine control at the antenatal clinic. Puerperal samples were obtained either in the delivery room immediately after parturition or on the 4th–5th day after parturition, when the patient left hospital or during routine investigation at the clinic about six weeks after parturition The distribution of the subjects according to the duration of pregnancy or the interval between parturition and sampling is given in Figs. 2 and 3. The material was unselected and the sera were collected during short periods when venous blood samples were obtained from all the mothers attending the antenatal clinic, or admitted to the obstetric ward. The samples collected on the 4th–5th day after parturition

were only from patients in which the puerperium was uncomplicated.

Sera from 374 females aged 12 to 50 years and included in a previously published investigation of the normal variation of the α_2-M (Ganrot and Scherstén 1967) served as reference in the calculation of the specific influence of pregnancy on the α_2-M concentration From this series 100 consecutive women aged 17–50 years were selected and used as a control group of non-pregnant women (smaller control groups) and are accounted for in Figs. 2 and 3

Methods

Determination of α_1 AT and α_2-M Determinations of the α_1 AT and of α_2-M were made by a quantitative immunochemical method described by Laurell (1966) The method consists of electrophoresis of serum dilutions in agarose gel containing specific antiserum against the serum protein to be determined. An antigen antibody precipitate forms whose length is proportional to the concentration of the antigen in the serum studied. The length of the zone of precipitation is measured in relation to corresponding lengths in a series of dilutions of a standard serum, and the concentration of the protein is given as a percentage of that of the standard serum. Specific antisera were obtained by immunisation of rabbits with highly purified preparations of α_1-AT and α_2-M respectively Anti-α_2-M was made specific by absorption with a purified preparation of Ig M and a macroglobulinfree serum fraction A pool of sera from 60 male blood donors served as a standard for the determinations

Calculation The α_1-AT-concentrations in all sera are given as percentages of the concentration in the standard serum. The α_2-M concentration was first expressed in the same way as a percentage of the concentration in the standard serum. In order to eliminate the effect of the variation with age and sex, the individual quotient was calculated between the value measured and the normal value for age-matched non-pregnant women The age-specific normal value was obtained from a smoothed normal curve

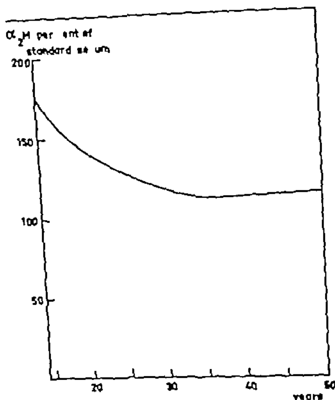


Fig. Normal value for α_2-M-concentration in females of different ages expressed as per cent of the concentration in the standard serum used.

for the α_2-M-concentration in the larger normal series (Fig. 1). The quotient was finally multiplied by 100. The values given denote the α_2-M-concentration as a percentage of the normal value for women corrected for the individual's age.

Results

α_1-AT-concentration in the serum during pregnancy. The α_1-AT concentration in the group of 100 non-pregnant women showed a median value which corresponded exactly to the concentration

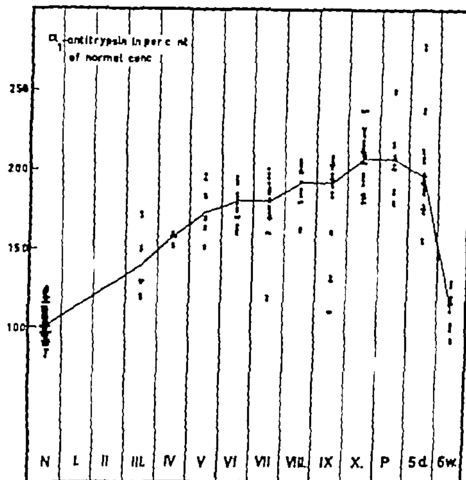


Fig. 2 α_1 AT-concentration in various groups expressed as per cent of the standard value. "N" normal group of 100 non-pregnant women, "I"–"X" groups of pregnant women in 1st–10th month of pregnancy P" group where samples were taken immediately after parturition. 5d and "6w groups where samples were collected 4–5 days after parturition and 6 weeks after parturition respectively The uninterrupted line joins the median values of the groups.

in standard serum from the male blood donors The values ranged from 56 % to 150 % of the concentration in the standard serum.

In all but three of the sera from pregnant women the α_1 AT concentration was found to be higher than that in the standard serum (Fig 2) The highest values were noted during the last trimester of pregnancy The median values in the various groups

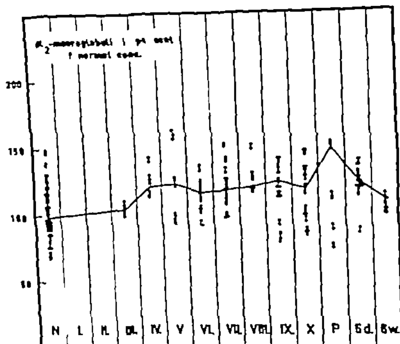


Fig. 3. α_2-M-concentration in various groups of the series for each case expressed as per cent of the calculated normal value according to age. All symbols as in Fig. 2. The uninterrupted line joins the median values of the groups.

of pregnant women increased mainly linearly with the duration of pregnancy and in the 10th month the median was 208 % of the concentration in the standard serum. The median value for α_1-AT-concentration immediately after parturition and that 4–5 days after parturition were almost the same as that for the 10th month of pregnancy. In sera obtained 6 weeks after parturition the α_1-AT-concentration had decreased markedly and the median value was then only 110 % of the concentration in the standard serum. In several of the subgroups of the series, both normal non-pregnant women and women who were pregnant or had been delivered the concentration was occasionally much lower than in most of the other women in the respective groups. The concentrations in these deviating sera in the normal group were 56–68 %

of the normal value During the latter part of pregnancy the concentration in this group of sera was somewhat higher than that in the standard serum In the group of sera from the 4th–5th day after parturition the concentration of the α_1-AT in one case was only 4 % of the normal value When the range of variation in the main population of each group during and after pregnancy was placed in relation to the median value of the respective groups it was found to be of the same order as in the normal group

The α_2-M-concentration in the serum during pregnancy The age of the women studied ranged from 16 to 39 years Within these limits the α_2-M-concentration varies widely and is reflected in the curve in Fig. 1 (Ganrot and Scherstén, 1967) The α_2-M-concentration was given first as a percentage of the concentration in the standard serum In order to obtain as long a specific measure as possible of the effect of pregnancy on the α_2-M-concentration the values obtained in each individual were converted to a relative value expressed as a percentage of the normal value for non pregnant women of corresponding ages.

The median value found for the group of 100 non pregnant women was 99 % of the normal value with a range of 64 % to 179 % For the various groups of pregnant women the average values noted were somewhat higher The median value increased during the first months of pregnancy so that in the 4th month it was about 120 % of normal and afterwards remained at that level during the rest of pregnancy (Fig 3) In the group of recently delivered women the range of variation was wide and the median value higher (148 %) than during pregnancy The group of sera from the 4th–5th day after parturition however contained on the average the same concentration of α_2-M and showed the same range of variation as before parturition Six weeks after parturition the concentration decreased to about 110 % of normal values

Discussion

In the determination of α_1-AT a specific immunochemical method was preferred to a non specific determination of the total antitrypsin activity of the serum In the choice between the two

specific methods for α_2-M-determination the immunochemical and the previously described TPE-method (Ganrot, 1966b) the former was preferred because it has been shown that pronounced lipaemia can interfere with the determination by the TPE method and most blood samples in the series were not obtained in the fasting state For control of the method however the TPE was also determined in all of the sera. Expressed as a per centage of the concentration in the standard serum the values obtained agreed with the immunochemically determined α_2-M values.

Faarvang (1959) studied the urinary excretion of a trypsin inhibitor called mingin during pregnancy and found a marked increase in some of the women, with a return to normal value within 4 weeks after parturition. In a later paper Faarvang and Lauritsen reported that the total trypsin inhibiting capacity of the serum was almost doubled during pregnancy (Faarvang and Lauritsen 1963) They ascribed this to an increase of the mingin which was believed not to be identical with α_1-AT and was called the stress- and glucocorticoid-regulated trypsin inhibitor (Faarvang, 1965) Normally the α_1-AT represents about 90 % of the total trypsin inhibiting capacity TIC of the serum. The increase of the α_1-AT to more than twice the normal value during pregnancy noted in the present investigation should thus cause approximately a 100 % increase of the TIC. It would thus appear that the above mentioned increase of the TIC was caused almost entirely by an increase of the α_1-AT and that the stress- and glucocorticoid-regulated trypsin inhibitor in the serum is identical with α_1-AT

The median value found for the α_1-AT-concentration in the control group of 100 non-pregnant women was equal to that in the standard serum pool obtained from 60 male blood donors. This lends further support to the assumption that the α_1-AT-concentration does not differ with sex. The group of sera which showed a much lower α_1-AT-concentration than the bulk of the sera in the respective group (corresponding to about 60 % of the median value) probably represents the heterozygotic carriers of the gene for α_1-AT-deficiency (Laurell and Eriksson 1963) The frequency of such carriers in the material agrees well with

that reported earlier for the same population (Eriksson 1965) It is clear from the results that the α_1-AT-concentration increased by 100 % during pregnancy also in these individuals The woman with 4 % of the normal concentration is also probably a homozygote for this gene with manifest α_1 AT-deficiency

What factor or factors cause the marked increase of the α_1-AT is not known Faarvangs work suggests that the α_1 AT-concentration is controlled by the steroid hormones It is therefore possible that the markedly changed steroid hormone balance during pregnancy is responsible for the increase in the α_1 AT The term "acute phase reactants has been used to designate serum proteins whose concentration increases in response to an inflammatory process (Kelley 1952) The discrepancy between the marked increase of the α_1 AT and the unchanged haptoglobin concentration during pregnancy without any demonstrable haptoglobin-consuming haemolysis is of theoretical interest. A systematic analysis of the situation during pregnancy of the other "acute phase reactants" may elucidate the regulation of this group of proteins

Delivery probably causes tissue damage of such an extent that an increase of the α_1-AT might be expected during the first few days after parturition That no further increase was seen on the 4th–5th day after parturition may mean that the α_1-AT increasing factor during pregnancy disappears immediately at parturition or that the increase during the latter part of pregnancy is already maximal. A possible explanation of the slight increase of the median value of the α_1-AT in the group of sera from 6 weeks after parturition may be due to the complications during lactation with fissures and small local inflammatory lesions.

The increase in the α_2-M during pregnancy was much less than the increase of the α_1 AT The values given also show a much smaller increase than that reported previously (Schlagetter and Schwick, 1961 Schumacher and Schlumberger 1963) This may be because the other factors which influence the α_2-M-concentration have been practically eliminated. If α_2-M concentration is given directly in per cent of the concentration of standard serum the median values for the group during the last two trimesters of pregnancy would be 160 % a value which

agrees well with what has been reported by previous workers in this field. The results show that even early in pregnancy the α_2-M concentration assumes a new steady state about 20% higher than before pregnancy and persists at that level at least some days after parturition. The mean value found for the group of sera taken immediately after parturition was 140.6% and is statistically probably significantly different ($0.05 > P > 0.01$) from the mean value for the group of sera from pregnant women in the 10th month (116.4%). The cause of this difference is obscure but restriction of fluid during labour might explain an increase in the α_2-M-concentration, but then a simultaneous increase in the α_1-AT-concentration should be expected. The median value for the group of sera taken 6 weeks after parturition suggests that the α_2-M-level had begun to return towards normal. It is not known what causes the change in the α_2-M-concentration during pregnancy. It might be the changed sex hormone activity. If so the increase might possibly be regarded as an accentuation of the normal sex difference with higher concentrations in females than in males. α_2-M is markedly increased during childhood and is possibly involved in the regulation of growth (Ganrot and Scherstén, 1967). Another possibility is therefore that the growth of the foetus in some way or other induces an increase of the α_2-M-concentration of the same type as that seen in children.

The biological functions of α_1 AT and α_2-M are not properly understood. Specific functions during pregnancy and in association with parturition have not been demonstrated. Both α_1-AT and the α_2-M can bind and inactivate trypsin (Schultze *et al.* 1962, Schultze *et al.* 1963, Mehl *et al.* 1964). The α_2-M, however acts as an inhibitor only of the protease activity of the trypsin while the esterase activity is stabilised against other trypsin inhibitors (Ganrot, 1966c). Both proteins can also bind and inhibit autoactivated plasmin (Schultze *et al.* 1963). The α_2-M represents the α_2-plasmin inhibitor (immediate inhibitor) while the α_1-AT probably represent the α_1-plasmin inhibitor (slow inhibitor) (Schultze *et al.* 1963, Norman and Hill, 1958). α_2-M has been shown to be capable of binding also a number of biologically active substances of protein nature (for reference see Ganrot and Scherstén, 1967). Obstructive pulmonary dis-

cases with disabling or fatal pulmonary emphysema as a result are common in α_1-AT-deficiency (Eriksson 1965) The case in which deficiency was observed (a 32 year old Para II) has, however not yet shown any pulmonary symptoms and pregnancy and delivery were normal

SUMMARY

The concentration of α_1-antitrypsin and of α_2-macroglobulin in serum were determined by immunochemical methods in 272 women during and after pregnancy The α_1-antitrypsin concentration increased mainly linearly with the duration of pregnancy until it was slightly more than twice the normal value at the time of parturition Also heterozygotic gene carriers for the α_1-antitrypsin deficiency doubled their α_1 antitrypsin concentration during pregnancy Six weeks after parturition the concentration was normal

The specific effect of pregnancy on the α_2-macroglobulin concentration was studied after elimination of the variation for age by giving the concentration in each individual in per cent of a normal value for non-pregnant women of corresponding age The α_2-macroglobulin concentration increased during the first four months of pregnancy up to 20 % above the original value and persisted at the elevated level until parturition.

Acknowledgement

This investigation was supported by grants from the Medical Faculty of the *University* of Lund.

REFERENCES

Eriksson S., Acta med. scand. *175* 197 1964

– Ibidem Suppl. 432 1965

Faarvang, H J., Acta endocrinol. *30* 85 1959

– Urinary trypsin inhibitor in man (thesis) Munksgaard Copenhagen 1965

Faarvang, H J and *Lauritsen O S.*, Nature *199* 290 1963

Ganrot P O Clin. chim. Acta 13 597 1966 a

– Ibidem *14* 493 1966 b

– Ibidem *13* 518 1966 c

Garrot P O and Scheraths B Clin. chim. Acta 15 3, 1967
Heide K., Helmburger M. and Haupt H Clin. chim. Acta 82 965
Herzig, W H Bull. schweiz. Akad. med. Wiss. 17 228 96
Holmberg, C. G and Laurell C.-B., Scand. J clin. Lab Invest. 3, 103 95
Kelley V C., J Pediat. 40 405, 952
Koch Fr Schultze H E and Schwick, G Arch. Kinderheilk. 59 3, 959
Krebs K. A., Klin. Wschr 7 584, 928
Laurell C.-B. and Eriksson S Scand. J. clin. Lab. Invest. 15, 32 1963
Clin. chim. Acta 395, 1965
Laurell C.-B., Analyt. Biochem. 5 45, 1966
Laurell C. B. and Garrot P O (unpublished) 1966
Lundh B Acta Univ Lund. II, No 26 965
Mehl J W O'Connell W and DeGroot J Science 45 821 964
Mehl J W Park, M. Y and O'Connell W Proc. Soc. exp Biol. Med. 122, 203, 966
Norman, P S and Hill B. M., J. exp. Med. 108 639 958
Schlegetter K. and Schwick, G Z. Geburtsh. Gynäk. 57 125 1961
Schultze H E., Heide K. and Haupt H Klin. Wschr 40 427 962
Schultze H. E., Heimburger N Heide K., Haupt H Störiko K. and Schwick H G Proc. 9th Congr europ Soc. Haemat. (Lisbon 963) (S Karger Basel/New York 1963) p. 315
Schumacher G and Schlumberger H. D Dtsch. med. Wschr 88 645, 963
Schönenberger M., Schmidtberger R. and Schultze H. E Z. Naturforsch. 3 b 76 958
Shulman, N R., J exp Med. 95, 605, 1952
Weiss, W A., Klin. Wschr 43, 273, 965

Received on July 1, 966

Brody Sam and Spetz, Sven, Acta obst. et gynec. scandinav 46, 138, 1967
From the Department of Obstetrics and Gynaecology University of Gothenburg, Gothenburg Sweden

PLASMA, EXTRACELLULAR AND INTERSTITIAL FLUID VOLUMES IN PREGNANCY COMPLICATED BY TOXAEMIA[1]

BY

SAM BRODY AND SVEN SPETZ

The total amount of body fluid shows considerable individual variations but there is good evidence that it increases during pregnancy (*Hytten* and *Leitch* 1964) Extensive studies have been carried out also on the respective roles played by the fractions constituting the different body fluid compartments

Particular attention has been devoted to the changes in plasma volume during the course of normal pregnancy (*e.g* *McLennan* and *Thouin* 1948 *Röttger* 1953 *Adams* 1954 *Gemzell et al* 1954 *Lund* and *Sisson* 1958 *Statzer* 1959 *Hytten* and *Paintin* 1963 *Rominger* 1964 *Verel Bury* and *Hope* 1965) A progressive increase until about the 34th week of gestation has been found. Thereafter a small decrease towards term has been observed. The proportional increase during normal pregnancy shows great individual variations ranging from 5 to 120 per cent. The total extracellular fluid comprising both the intravascular (plasma volume) and extravascular parts (interstitial fluid) has also been studied This fraction has been reported to increase by about 2 to 6 litres during pregnancy (*Friedberg*, 1958 *Röttger* 1953 *Mac Gillivray* 1961)

In cases of mild pre-eclampsia *Dieckmann* (1936) found the plasma volume to be of the same order of magnitude as during

[1] This study was supported by a grant from the Swedish Medical Research Council.

normal pregnancy In severe cases however he found decreased values In principle, this opinion was supported by *Freis* and *Kenny* (1948) *Friedberg* (1958 1961) and *Cope* (1958 1961) In contrast *Rominger* (1964) observed an increased blood volume in patients with toxaemia of pregnancy as compared with the levels recorded in normal pregnancy

Most evidence indicates an increase in the extravascular fluid in association with toxaemia of pregnancy *Freis* and *Kenny* (1948) and *Friedberg* (1958, 1961) maintain that there is a very marked increase in the interstitial fluid, whereas the intracellular fluid apparently is constant. *MacGillivray* (1961) also found an abnormally high retention of water in such patients. He suggested however that the accumulation of fluid was mainly intra cellular

This brief survey of our present state of knowledge in this field of clinical research indicates some inconsistency of the reports in the literature, both as to the question of possible deviations during toxaemia of pregnancy in the amounts of extracellular fluid, plasma volume, and interstitial fluid as compared with normal conditions and as to the magnitude of such changes. In part, the present situation has arisen as a consequence of conclusions drawn either from inadequate material or from series submitted to incomplete statistical analysis.

With this in mind we have attempted to gain additional insight into these problems and have therefore undertaken the present study on the distribution of the total extracellular fluid the plasma volume and the interstitial fluid during pregnancy with particular reference to the evaluation of the conditions in patients suffering from toxaemia of pregnancy

Material

Patients with toxaemia of pregnancy For the diagnosis of pre-eclampsia the definition and classification given by the American Committee on Maternal Welfare was followed. However at least two of the symptoms albuminuria, hypertension and oedema were required for the diagnosis of pre-eclampsia As a rule the patients were studied on the day following the admission to the

Table I. *Mean Weights of Infants and of Placentas in Normal and Toxaemic Pregnancies*

Weeks of Pregnancy	Normal Pregnancy			Pre-eclampsia		
	32–34	35–37	38–40	32–34	35–37	38–40
Mean weight of the infants (gm)	3603	3170	3369	1653	2519	3258
Standard deviation for mean value	±451	±359	±657	±341	±678	±575
Mean weight of the placentas (gm)	656	598	627	450	463	544
Standard deviation for mean value	±103	±122	±124	±164	±108	±117

The subjects are classified according to gestational time at which the analysis were carried out. All patients delivered within ±14 days of the expected date for delivery

Table II. *Weight of Infants and Placentas. Statistical Significance of Differences (P)*

Weeks of Pregnancy	32–34	35–37	38–40
Weight of infants	<0.001	$0.01>P>0.001$	>0.05
Weight of placentas	$0.05>P>0.01$	$0.05>P>0.01$	$0.05>P>0.01$

hospital and before any treatment had been given The time of gestation was calculated from the first day of the last menstrual period. 34 patients (25 primigravidae 9 multigravidae patients) were examined between the 32nd–40th week of gestation. The patients were 17–37 years old, the mean being 25 years In Table I are seen the mean weights of the newborn children and of the placentas, in Table II the results of the statistical treatment of the values In 8 of the 34 cases the pre-eclampsia was classified as severe

Pregnant controls As controls 46 normal pregnant patients with gestational period varying from 32 to 40 weeks were examined once The ages varied between 18 and 42 years the mean being 26 years. Sixteen women were primigravidae and 30 were multigravidae with one or more previous normal pregnancies and deliveries. The mean weights of the children and of the placentas are seen in Table I.

Non-pregnant controls. Forty-five non-pregnant women were examined once the mean age being 22 years with a range of 16–38 years. Most of these women had never been pregnant.

Methods

Plasma volume This was determined by use of Evans blue dye (T 1824) The test was performed in the morning, the patients having fasted for 8 hours. With the patient resting in bed a blood sample was taken from a cubital vein. Five ml of a 0.3 per cent solution of the dye was then injected intravenously the syringe being washed with saline. After 15 minutes blood was taken from the other arm. The concentration of the Evans blue dye in the 15-minute sample was compared with a standard made up in the pre-injection serum of each patient, the optical density being estimated spectrophotometrically at the wave length of 620 mμ. The total plasma volume and the plasma volume per kg of body weight were then calculated.

Extracellular fluid. This was estimated by the method described by *Franckson et al.* (1962) determining the disappearance rate of injected glucose. Fifty ml of a 50 per cent solution of glucose was injected rapidly into a cubital vein The blood glucose concentration was then determined every 15th minute by means of the ortho-toluidin-method described by *Hultman* (1959) The glucose assimilation coefficient was calculated by means of plot ting the blood glucose concentration against time on a logarithmic scale To determine the diffusion space of injected glucose (Vg) the following formula was applied

$$Vg = \frac{Q}{A - C_0} \text{ where}$$

Q = quantity of glucose injected.
A – value obtained by means of extrapolating the semilogarithmic line to time zero
C_0 the blood glucose concentration before injection

The total extracellular fluid and the amount per kg of body weight were then calculated.

Table III. *Plasma Volume Total and per kg of Body Weight*

Weeks of Pregnancy	Non Pregnant	Normal Pregnancy			Pre-eclampsia	
		32–34	35–37	38–40	32–34	35–37
Number of cases	45	8	9	29	5	15
Mean value total amount (ml)	2908	4373	4214	4226	3838	3827
Standard deviation for mean value	±426	±482	±726	±510	±481	±450
Mean value ml per kg of body weight	54	65	63	60	59	56
Standard deviation for mean value	±2.2	±8 8	±9.6	±5.9	±3.6	±5.1

Table IV *Plasma Volume Statistical Significance of Differences (P)*

Weeks of Pregnancy	32–34	35–37	38–40
Total plasma volume			
Non-pregnant—pregnant	<0.001	<0.001	<0.001
Normal pregnancy—pre-eclampsia	0 05>P>0.01	>0.05	>0.05
Plasma volume ml per kg of body weight			
Non-pregnant—pregnant	<0.001	0.05>P>0 01	0 01>P
Normal pregnancy—pre-eclampsia	>0.05	0.05>P>0.01	>0 05

Interstitial fluid This was calculated by subtracting the plasma volume from the amount of the total extracellular fluid.

Statistical analysis. For the statistical treatment conventional methods were applied Analysis of variance was used to test the significances of differences between different groups (*Bonnier* and *Tedin* 1940) For the evaluation of the P values obtained the following significance levels have been adopted $P<0\ 001=$ $=$highly significant $P<0\ 01=$significant $P<0\ 05=$almost significant $P>0\ 05=$not significant.

Table V *Extracellular Fluid, Total and per kg of Body Weight*

Weeks of Pregnancy	Non Pregnant	Normal Pregnancy			Pre-eclampsia		
		32 34	35–37	38–40	32 34	35–37	38–40
Number of cases	45	8	9	29	5	13	13
Mean value total amount (litres)	14.1	18.6	18.7	17.5	18.1	17.3	17.5
Standard deviation for mean value	± 1.80	± 4.65	± 2.95	± 3.21	± 3.18	± 2.46	± 3.68
Mean value ml per kg of body weight	262	274	280	245	275	252	229
Standard deviation for mean value	± 33	± 64	± 31	± 45	± 40	± 27	± 49

Table VI. *Extracellular Fluid. Statistical Significance of Differences (P)*

Weeks of Pregnancy	32 34	35–37	38–40
Total amount:			
Non-pregnant—pregnant	< 0.001	< 0.001	< 0.001
Normal pregnancy—pre-eclampsia	> 0.05	> 0.05	> 0.05
Amount ml per kg of body weight.			
Non-pregnant—pregnant	> 0.05	> 0.05	0.05 > P > 0.01
Normal pregnancy—pre-eclampsia	> 0.05	> 0.05	> 0.05

Results

In order to evaluate possible differences between normal pregnant women and patients with toxaemia of pregnancy the patients were divided in groups according to the time of gestation at which the analyses were performed (32nd–34th week, 35th–37th week, and 38th–40th week) and the mean values calculated for the results obtained on the patients in each group In this paper no differentiation has been made between the mild and severe cases of pre-eclampsia.

Table III. *Plasma Volume Total and per kg of Body Weight*

Weeks of Pregnancy	Non Pregnant	Normal Pregnancy			Pre-eclampsia		
		32–34	35–37	38–40	32–34	35–37	38–
Number of cases	45	8	9	29	5	15	1
Mean value total amount (ml)	2905	4373	4214	4226	3838	3827	426
Standard deviation for mean value	± 426	± 482	± 726	± 510	± 481	± 450	± 63
Mean value ml per kg of body weight	54	65	63	60	59	56	5
Standard deviation for mean value	± 2.2	± 8.8	± 9.6	± 5.9	± 3.6	± 5.1	±

Table IV *Plasma Volume Statistical Significance of Differences (P)*

Weeks of Pregnancy	32–34	35–37	38–40
Total plasma volume			
Non-pregnant—pregnant	< 0.001	< 0.001	< 0.001
Normal pregnancy—pre-eclampsia	0.05 > P > 0.01	> 0.05	> 0.05
Plasma volume ml per kg of body weight			
Non-pregnant—pregnant	< 0 001	0.05 > P > 0.01	0.01 > P > 0.0
Normal pregnancy—pre-eclampsia	> 0.05	0.05 > P > 0 01	> 0.05

Interstitial fluid. This was calculated by subtracting the plasma volume from the amount of the total extracellular fluid.

Statistical analysis. For the statistical treatment conventional methods were applied. Analysis of variance was used to test the significances of differences between different groups (*Bonnier* and *Tedin* 1940) For the evaluation of the P values obtained the following significance levels have been adopted $P < 0\ 001 =$ = highly significant $P < 0\ 01 =$ significant $P < 0\ 05 =$ almost significant $P > 0\ 05 =$ not significant.

and the amounts per kg of body weight show somewhat lower mean values in comparison with normal pregnancy This would seem to be the case at least between the 32nd–37th week of gestation. However the differences are not statistically significant (Table IV)

Extracellular fluid The number of cases studied the mean values and their standard deviations are seen in Table V In Table VI the results of the statistical analysis are presented. There is a highly significant difference in the total amount of extracellular fluid between nonpregnant subjects and pregnant women. On the other hand, when the amount of extracellular fluid is calculated per kg of body weight the difference between the groups is not significant Between the 38th–40th week however the difference is almost significant. Thus the amount of extracellular fluid seems to increase in parallel with the gain in weight during pregnancy At term the total extracellular fluid shows an increase of between 3 to 5 litres in comparison with the non-pregnant subjects

No marked changes have been found in pregnancy complicated by toxaemia in comparison with normal pregnancy the extra cellular fluid exhibits no statistically significant change in tox aemic patients.

Interstitial fluid In Table VII the mean values and their stand ard deviations for the amount of interstitial fluid in the different groups have been summarized. Table VIII shows the results of the statistical analysis. The total amount increases during preg- nancy by about 2 to 4 litres the differences in the values found in pregnant and non-pregnant subjects being highly significant. When the interstitial fluid is calculated per kg of body weight the statistical significance disappears except between the 38th–40th week. Thus the interstitial fluid during pregnancy increases in parallel with the gain in body weight except during the last three weeks of gestation when a relative decrease is found (Table VII) Values obtained during normal pregnancy and in patients with toxaemia do not differ either as regards the total amounts or the amounts per kg of body weight.

Table VII. *Interstitial Fluid Total and per kg of Body Weight*

Weeks of Pregnancy	Non Pregnant	Normal Pregnancy 32–34	35–37	38–40	Pre-eclampsia 32–34	35–37	38-
Number of cases	45	8	9	29	5	13	13
Mean value total amount (litres)	11.2	14.2	14.5	13.3	14.0	13.4	13
Standard deviation for mean value	± 1.58	± 4.64	± 2.56	± 2.72	± 3.00	± 2.73	± 3
Mean value ml per kg of body weight	207	209	217	188	213	196	174
Standard deviation for mean value	± 37	± 65	± 27	± 39	± 34	± 24	± 45

Table VIII *Interstitial Fluid. Statistical Significance of Differences (P)*

Weeks of Pregnancy	32–34	35–37	38–40
Total amount.			
Non-pregnant—pregnant	< 0.001	< 0.001	< 0.001
Normal pregnancy—pre-eclampsia	> 0.05	> 0.05	0.05 > P > 0.0
Amount ml per kg of body weight			
Non-pregnant—pregnant	> 0.05	> 0.05	0.01 > P > 0.0
Normal pregnancy—pre-eclampsia	> 0.05	> 0.05	> 0.05

Plasma volume Table III shows the number of cases studied in each group the mean values and their standard deviations In Table IV the statistical significances of the differences between the groups have been tabulated. The increase in plasma volume during pregnancy is obvious and the differences between the non pregnant and the pregnant groups are highly significant. The values obtained during normal pregnancy after the 32nd week are quite constant no decrease being observed towards term in this series In the pre-eclamptic groups the total plasma volume

analyses to be of any practical value *Friedberg* (1958 1961) examined 16 patients with toxaemia of pregnancy and maintained that the plasma volume was clearly lower than during normal pregnancy *Rominger* (1964) examined 10 patients with mild and severe pre-eclampsia. He found the proportionate increase in blood volume to be greater than during normal pregnancy the individual values also being very high.

The values for plasma volume found in the present series of cases with toxaemia are as a rule somewhat lower than values for normal pregnancies of corresponding gestational age the differences however are not statistically significant. But it should be mentioned that the difference between pre-eclamptic patients of the 32nd–34th week group and normally pregnant women at the 32nd–34th week of gestation is almost significant. This may possibly be due to the fact that most of the severe cases of pre-eclampsia are found in this early group

The different groups of pregnant patients do not differ significantly as regards their mean age. On the other hand significant differences were observed with respect to the birth weights of the infants in the 32nd to 37th week groups. No such difference was found in the 38th to 40th week group This emphasizes the fact that the most serious cases of toxaemia appeared early Also with regard to the weights of the placentas, almost significant differences were seen between all the normal and pre-eclamptic groups.

The present series is too small to be divided into cases with mild and severe pre-eclampsia. However the severe cases do not seem to have lower plasma volumes than the mild ones. In some cases the plasma volume was estimated repeatedly at weekly intervals during the course of treatment with diuretic and hypotensive drugs. In spite of the fact that the symptoms of pre-eclampsia were improved, e.g a decrease in the mean blood pressure level and visible oedema and a reduction of weight no significant changes in the results were noticed the values obtained were quite constant. We are fully aware of the desirability to carry out serial examinations during pregnancy to eliminate the role played by individual variations. However such serial examinations would have to be performed on a very large group of

Discussion

To determine the plasma volume during pregnancy the use of Evans blue dye seems to be a simple and accurate method. Equilibrium in the plasma is reached within 10 minutes the dye being attached to the plasma albumin fraction The amount of the dye leaving the circulation during the first 10–15 minutes after the injection is negligible. The dye can be extracted from the serum or be subject to direct measurement in the serum from fasting subjects as was the case in the present study The values obtained by different investigators using the Evans blue method differ somewhat due to minor differences in the technique used. The absolute values for the plasma volume, however seem to be of minor interest in comparison with the relative changes occurring during the course of pregnancy, and in comparison with possible differences between normal pregnant patients and those suffering from toxaemia of pregnancy The salient point appears to be that the different groups are examined by the same investigators.

Earlier investigators indicate that in pregnancy complicated by toxaemia the plasma volume as a rule is lower than during normal pregnancy The individual variations however seem to be pronounced and this fact somewhat clouds the picture. *Dieckmann* (1936) found low values for the plasma volume in severe pre-eclampsia and eclampsia. *Freis* and *Kenny* (1948) examined three patients with severe pre-eclampsia and two patients with eclampsia. The total plasma volume varied between 1927 and 5320 ml In seven patients in the third trimester of normal pregnancy total plasma volume varied between 3595 and 4950 ml. The plasma volume calculated per kg of body weight varied between 37 0 and 72.9 ml with a mean value of 44.3 ml in the pre-eclamptic and eclamptic group During normal pregnancy the corresponding values ranged were 47 0 to 70.5 ml with a mean value of 59 1 ml. *Cope* (1958 1961) studied 14 cases with pre-eclampsia the values varying between 2320 and 4030 ml. The average plasma volume per kg of body weight was 43 3 ml in comparison with 47 0 ml during normal pregnancy *Cope* (1961) concluded that the total plasma volume was the most representative parameter although individual variations were too large for these

obtained using the sodium thiocyanate technique (*Franckson et al* 1962) In earlier investigations a considerable overlap of the values in normal and toxaemic pregnancy have been demonstrated. Changes in plasma volume and in the amount of interstitial fluid have generally been assumed to be associated with the appearance of some of the symptoms of pre-eclampsia e.g oedema and oliguria. If such changes were of importance the differences in these parameters between normal and pre-eclamptic pregnancy should be statistically significant. In the present study however no significant changes as regards total extracellular fluid, plasma volume and interstitial fluid have been found between these groups If there is some abnormal retention of fluid in toxaemic subjects this accumulation probably will be located intracellularly

SUMMARY

1. Plasma volume extracellular and interstitial fluid have been estimated in 34 cases with mild and severe pre-eclampsia As controls 45 non-pregnant women and 46 normal pregnant subjects were examined. The pregnant women were classified according to the length of gestation and mean values calculated for each period. Statistical analysis of the results has been performed.
2. Plasma volume was measured by use of Evans blue dye The difference between non-pregnant and pregnant women was highly significant. The plasma volume, calculated as total amount or amount per kg of body weight, was not found to differ significantly between normal pregnant subjects and pre-eclamptic women.
3. The total amount of extracellular fluid was measured by estimating the disappearance rate of injected glucose A highly significant difference was found between non-pregnant and pregnant subjects When the amount of extracellular fluid was calculated per kg of body weight no significant difference was found between these two groups. No statistically significant differences were found between normal pregnant women and pre-eclamptic patients with regard to the total amount

pregnant women as only a minor fraction develops the clinical picture of pre-eclampsia.

The total extracellular fluid in patients with pre-eclampsia has been investigated by *Freis* and *Kenny* (1948) by means of sodium thiocyanate They found high values the mean being 321 ml per kg of body weight in comparison with 245 ml per kg during normal pregnancy However a considerable scatter of the values was found. *Friedberg* (1958 1961) examined the water distribution in 16 patients with toxaemia. No increase of the intracellular water content was found. The extracellular water was increased. In some cases the plasma volume was found to be low fluid being stored in the interstitial tissue These results indicated a difference in fluid distribution between normal pregnant women and patients with toxaemia of pregnancy They were interpreted as evidence in favour of the assumption that during normal pregnancy there is an increase both in plasma volume and interstitial fluid whereas in toxaemia the increase in total body fluid would be caused only by the interstitial fluid, the plasma volume being decreased. *MacGillivray* (1961) in 17 patients with mild and 14 patients with severe pre-eclampsia measured total body water and total exchangeable chloride by means of deuterium oxide and ^{82}Br respectively In mild and severe cases of pre-eclampsia with oedema he found that fluid retention was over 6 litres more than that found in normal pregnancy In cases with mild pre-eclampsia without clinical oedema this excess retention of fluid amounted to about 9 litres and in cases with severe pre-eclampsia without oedema the excess retention amounted to 4.5 litres. The marked retention of fluid in cases without obvious clinical oedema was supposed to indicate an intracellular accumulation of fluid. This accumulation of fluid was not accompanied by a concomitant retention of sodium or chloride

The total body fluid thus seems to be increased in patients with toxaemia in comparison with normal pregnancy although there are conflicting views about the locale where the retention of fluid occurs whether intracellularly or in the interstitial space

In the present study the extracellular fluid was measured by estimating the diffusion rate of injected glucose This method has been shown to give results which are in agreement with those

Spetz, Sven, and Brody, Sam, Acta obst. et gynec. scandinav. 46, 151, 1967
From the Department of Obstetrics and Gynaecology University of Gothenburg, Gothenburg, Sweden

SERUM PROTEINS IN PREGNANCY COMPLICATED BY TOXAEMIA[1]

BY

SVEN SPETZ AND SAM BRODY

Many investigations have been carried out concerning the concentration of serum proteins and their different fractions both in normal and toxaemic pregnancy (*Lagercrantz* 1945–1946 Freis and Kenny 1948 Moore Du Pan and Buxton, 1949 *Scrimshaw* and *Alling*, 1949 *Coryell et al.* 1950 *Mack* 1960 *Reboud et al.*, 1963 *de Alvarez* and *Afonso* 1964 *Hytten* and *Leitch* 1964 *Bronsema* 1965) The results, as a rule, have been presented in terms of the amount of protein per unit of serum or as the relative proportion of a particular protein fraction.

The objectives underlying these studies have been several, e g the elucidation of the problem whether quantitative changes in the serum proteins precede or follow the clinical manifestations of toxaemia of pregnancy and, if so whether there is any relationship between the severity of the disease and these laboratory findings.

It would seem, however that certain relationships may be spurious whereas others may be overlooked when the results are expressed in the terms given above. Sudden shifts in the degree of haemoconcentration may bring about changes in the protein concentration which are in effect, secondary to other pathologic processes. Furthermore differences recorded in the relative proportion of a serum protein fraction may be caused by changes in one or several other protein fractions

[1] This study was supported by a grant from the Swedish Medical Research Council.

[illegible]

of extracellular fluid or the amount calculated per kg of body weight

4 The total amount of interstitial fluid increases during pregnancy and the values obtained during pregnancy differ significantly from those found in non-pregnant women. Between the 38th–40th week of gestation the amount of interstitial fluid per kg of body weight differs significantly between non-pregnant and pregnant subjects. The differences between the 32nd–37th week groups are not significant. In pregnancy complicated by toxaemia no significant changes were found in comparison with normal pregnancy

REFERENCES

Adams J Q., Am. J Obstet. Gynec. *67* 741 1954

Bonnier G and *Tedin O.*, Biologisk variationsanalys Stockholm 1940

Cope I J Obstet. Gynaec. Brit. Emp *65* 877 1958

Cope I., J Obstet. Gynaec. Brit. Cmwlth. *68* 413 1961

Dieckmann W J Am. J Obst. Gynec. *32* 927 1936

Franckson J R. M Ooms H Bellens R. Conard, V and *Bastenie P A.*, Metabolism *11* 482, 1962

Freis E. D and *Kenny J F.*, J Clin. Invest. *27* 283 1948

Friedberg, V Zbl. Gynäk. *80* 159 1958

Friedberg, V., Anaesthesist, *10* 334 1961

Gemzell C. A. Robbe H., and *Sjöstrand T.*, Acta obst. gyn. scand., 33 289 1954

Hultman E. Nature *183* 108 1959

Hytten F E. and *Paintin D B.* J Obstet. Gynaec. Brit. Cmwlth. *70* 402, 1963

Hytten F E. and *Leitch I* The Physiology of Human Pregnancy Blackwell Scientific Publications Oxford, 1964

Lund, C. J and *Sisson T R. C.* Am. J Obstet. Gynec. *76* 1013 1958

MacGillivray I., Pathologia et microbiologia *24* 639 1961

McLennan C. E. and *Thouin L. G* Am. J Obstet. Gynec. *55* 189 1948

Rominger C. J The American Surgeon *30* 357 1964

Rötger H Arch. Gynäk. *184* 59 1953

Statzer D E. Obstet. and Gynec. *14* 37 1959

Verel D., *Bury J D* and *Hope A.* Clin. Sci. *15* 1 1965

Received on May 18th, 1966

The different protein fractions were calculated and expressed as the amount per unit of serum, as the relative percentages of the total serum protein as the total amount of circulating protein and as the amount per kg of body weight.

Statistical analysis. The results obtained were examined by means of conventional statistical methods (*Bonnier* and *Tedin* 1940) The following significance levels for differences were adopted

$P < 0.001$ = highly significant· $P < 0.01$ = significant
$P < 0.05$ = almost significant $P > 0.05$ = not significant.

Results

The actual duration of gestation (32nd–40th week) in the present study was divided into three 3-week periods (32nd–34th week 35th–37th week and 38th–40th week) and mean values cal culated for all the results of analyses carried out in each period. In the following presentation of the results the patients classified as mild and severe cases of pre-eclampsia have been taken together The reason for this is that the number of severe cases is too small to constitute a separate group for statistical purposes.

Total serum protein Table I shows the results obtained and Table II summarizes the results of the statistical analysis. The protein concentration per 100 ml of serum is lower during pregnancy in comparison with the non-pregnant state and the dif ferences are highly significant. No significant differences, how ever are found between normal and toxaemic pregnancies.

The total amount of circulating protein is higher in pregnant than in non-pregnant women and the differences are mostly highly significant. No marked changes are found in toxaemia in comparison with normal pregnancy except for the 35th–37th week of gestation, when there is an almost significant difference.

The total serum protein calculated as the amount per kg of body weight does not seem to differ significantly between non-pregnant and pregnant subjects Between the 35th and 40th week, however the values obtained are somewhat lower in preg nant patients and the differences are almost significant. Between the 35th and 37th week significantly lower values are obtained in

For a complete evaluation of these problems in the clinical conditions under discussion it appears that certain other dimensions also should be calculated such as the total amount of circulating serum protein or its subfractions and the amount of these serum constituents related to body weight. We are only aware of one paper dealing with this particular aspect namely that of *Freis* and *Kenny* (1948) Even in this work, however the analytical data were restricted to those concerning the total serum protein and no attempts were made to estimate its subfractions.

In a recent study (*Brody* and *Spetz* 1967) we have estimated the magnitude of different body fluid fractions including plasma volume in a number of non pregnant subjects normal pregnant women and patients suffering from pre-eclampsia. During this work the total serum protein and some different serum protein fractions were also determined. This paper is a report of these results

Material

Thirty four patients with toxaemia of pregnancy and 46 normal pregnant women were examined between the 32nd and 40th week of gestation For a more detailed description of the material and criteria for classification the reader is referred to *Brody* and *Spetz* (1967)

As non pregnant controls 45 healthy women were examined.

Methods

The different serum protein fractions were separated by means of paper electrophoresis (Spinco Model R) Using a veronal buffer pH 8 6 the separation of the fractions was allowed to proceed for 16 hours at 5 Ma The papers were stained with bromphenol blue and the different fractions eluted by means of a 0 5 % solution of sodium carbonate The optical density was then read by means of a Zeiss spectrophotometer at 590 mμ

The total serum protein was determined by the Biuret method (*Lehmann* 1944 *Lang* and *Lehnartz* 1953)

Plasma volume was determined by means of Evans blue dye (see *Brody* and *Spetz* 1967)

The different protein fractions were calculated and expressed as the amount per unit of serum, as the relative percentages of the total serum protein, as the total amount of circulating protein and as the amount per kg of body weight.

Statistical analysis. The results obtained were examined by means of conventional statistical methods (*Bonnier* and *Tedin* 1940) The following significance levels for differences were adopted

$P < 0.001$ = highly significant $P < 0.01$ = significant
$P < 0.05$ = almost significant $P > 0.05$ = not significant.

Results

The actual duration of gestation (32nd–40th week) in the present study was divided into three 3-week periods (32nd–34th week 35th–37th week and 38th–40th week) and mean values calculated for all the results of analyses carried out in each period In the following presentation of the results the patients classified as mild and severe cases of pre-eclampsia have been taken together The reason for this is that the number of severe cases is too small to constitute a separate group for statistical purposes

Total serum protein. Table I shows the results obtained and Table II summarizes the results of the statistical analysis. The protein concentration per 100 ml of serum is lower during pregnancy in comparison with the non-pregnant state and the differences are highly significant. No significant differences, however are found between normal and toxaemic pregnancies.

The total amount of circulating protein is higher in pregnant than in non-pregnant women and the differences are mostly highly significant. No marked changes are found in toxaemia in comparison with normal pregnancy except for the 35th–37th week of gestation when there is an almost significant difference

The total serum protein calculated as the amount per kg of body weight does not seem to differ significantly between non-pregnant and pregnant subjects. Between the 35th and 40th week, however the values obtained are somewhat lower in pregnant patients and the differences are almost significant. Between the 35th and 37th week significantly lower values are obtained in

For a complete evaluation of these problems in the clinical conditions under discussion it appears that certain other dimensions also should be calculated, such as the total amount of circulating serum protein or its subfractions and the amount of these serum constituents related to body weight. We are only aware of one paper dealing with this particular aspect, namely that of *Freis* and *Kenny* (1948). Even in this work, however, the analytical data were restricted to those concerning the total serum protein and no attempts were made to estimate its subfractions.

In a recent study (*Brody* and *Spetz* 1967) we have estimated the magnitude of different body fluid fractions, including plasma volume, in a number of non-pregnant subjects, normal pregnant women, and patients suffering from pre-eclampsia. During this work, the total serum protein and some different serum protein fractions were also determined. This paper is a report of these results.

Material

Thirty-four patients with toxaemia of pregnancy and 46 normal pregnant women were examined between the 32nd and 40th week of gestation. For a more detailed description of the material and criteria for classification the reader is referred to *Brody* and *Spetz* (1967).

As non pregnant controls 45 healthy women were examined.

Methods

The different serum protein fractions were separated by means of paper electrophoresis (Spinco Model R). Using a veronal buffer pH 8.6, the separation of the fractions was allowed to proceed for 16 hours at 5 Ma. The papers were stained with bromphenol blue and the different fractions eluted by means of a 0.5 % solution of sodium carbonate. The optical density was then read by means of a Zeiss spectrophotometer at 590 mμ.

The total serum protein was determined by the Biuret method (*Lehmann* 1944, *Lang* and *Lehnartz* 1953).

Plasma volume was determined by means of Evans blue dye (see *Brody* and *Spetz* 1967).

Table III. Serum Albumin (Relative Percentage: g per 100 ml of Serum, Total Circulating Amount. Amount per kg of Body Weight)

Weeks of Pregnancy	Non Pregnant	Normal Pregnancy			Pre-eclampsia		
		32–34	35–37	38–40	32–34	35–37	38–40
Number of observations	45	8	9	29	5	15	14
Mean value (relative percentage)	61.9	52.7	55.2	55.2	51.1	51.0	52.9
Standard deviation for mean value	±5.25	±5.37	±3.19	±4.55	±4.57	±5.15	±5.77
Mean value (g per 100 ml of serum)	4.6	3.3	3.6	3.5	3.1	3.1	3.4
Standard deviation for mean value	±0.79	±0.48	±0.37	±0.49	±0.50	±0.89	±0.54
Mean value (total amount, g)	134.3	145.3	150.2	145.8	119.2	119.6	144.5
Standard deviation for mean value	±26.91	±27.45	±17.91	±21.44	±23.53	±24.38	±25.96
Mean value (g per kg of body weight)	2.5	2.2	2.3	2.1	1.8	1.7	1.9
Standard deviation for mean value	±0.17	±0.35	±0.65	±0.56	±0.47	±0.51	±0.46

toxaemic patients in comparison with normal pregnant patients. In other periods however no marked differences could be established between normal pregnant and toxaemic women.

Serum albumin. The results are condensed in Tables III and IV. The albumin concentration, expressed per unit of serum or as a percentage of the total serum protein is lower during pregnancy and the differences are highly significant. As regards these parameters no significant changes are found in association with toxaemia of pregnancy as compared with normal pregnancy.

The total amount of circulating albumin does not change significantly in pregnant subjects in comparison with non-pregnant women. Between the 38th and 40th week the total amount, how-

Table I. *Total Serum Protein (g per 100 ml of Serum Total Circulating Amount Amount per kg of Body Weight)*

Weeks of Pregnancy	Non Pregnant	Normal Pregnancy			Pre-eclampsia		
		32–34	35–37	38–40	32–34	35–37	38–40
Number of observations	45	8	9	29	5	15	14
Mean value (g per 100 ml of serum)	7.4	6.3	6.5	6.3	6.1	6.2	6.5
Standard deviation for mean value	± 1.20	± 0.75	± 0.49	± 0.45	± 0.99	± 0.72	± 0.58
Mean value (total amount, g)	216.2	277.2	271.8	265.1	232.8	234.2	274.9
Standard deviation for mean value	± 38.31	± 42.47	± 36.30	± 34.33	± 34.25	± 31.28	± 49.74
Mean value (g per kg of body weight)	4.0	4.1	4.1	3.7	3.6	3.4	3.7
Standard deviation for mean value	± 0.10	± 0.66	± 0.56	± 0.79	± 0.80	± 0.64	± 0.24

Table II. *Total Serum Protein (Statistical Significance of Differences (P))*

Weeks of Pregnancy	32–34	35–37	38–40
g per 100 ml of serum.			
Non-pregnant—pregnancy	< 0.001	< 0.001	< 0.001
Normal pregnancy—pre-eclampsia	> 0.05	> 0.05	> 0.05
Total circulating amount:			
Non-pregnant—pregnancy	< 0.001	0.01 > P > 0.001	< 0.001
Normal pregnancy—pre-eclampsia	> 0.05	0.05 > P > 0.01	> 0.05
g per kg of body weight:			
Non-pregnant—pregnancy	> 0.05	0.05 > P > 0.01	0.05 > P > 0.01
Normal pregnancy—pre-eclampsia	> 0.05	0.01 > P > 0.001	> 0.05

Table III. *Serum Albumin (Relative Percentage g per 100 ml of Serum Total Circulating Amount Amount per kg of Body Weight)*

Weeks of Pregnancy	Non Pregnant	Normal Pregnancy			Pre-eclampsia		
		32 34	35–37	38–40	32 34	35–37	38–40
Number of observations	45	8	9	29	5	15	14
Mean value (relative percentage)	61.9	52.7	55.2	55.2	51.1	51.0	52.9
Standard deviation for mean value	±5.25	±5.37	±3.19	±4.55	±4.57	±5.15	±5.77
Mean value (g per 100 ml of serum)	4.6	3.3	3.6	3.5	3.1	3.1	3.4
Standard deviation for mean value	±0.79	±0.48	±0.37	±0.49	±0.50	±0.89	±0.54
Mean value (total amount, g)	134.2	145.3	150.2	145.8	119.2	119.6	144.5
Standard deviation for mean value	±26.91	±27.45	±17.91	±21.44	±23.53	±24.36	±25.96
Mean value (g per kg of body weight)	2.5	2.2	2.3	2.1	1.8	1.7	1.9
Standard deviation for mean value	±0.17	±0.35	±0.65	±0.56	±0.47	±0.51	±0.46

toxaemic patients in comparison with normal pregnant patients. In other periods however no marked differences could be established between normal pregnant and toxaemic women.

Serum albumin. The results are condensed in Tables III and IV The albumin concentration expressed per unit of serum or as a percentage of the total serum protein is lower during pregnancy and the differences are highly significant. As regards these parameters no significant changes are found in association with toxaemia of pregnancy as compared with normal pregnancy

The total amount of circulating albumin does not change significantly in pregnant subjects in comparison with non-pregnant women. Between the 38th and 40th week the total amount, how-

Table I. *Total Serum Protein (g per 100 ml of Serum Total Circulating Amount Ance: per kg of Body Weight)*

	Non Pregnant	Normal Pregnancy			Pre-eclampsia		
Weeks of Pregnancy		32–34	35–37	38–40	32–34	35–37	38–40
Number of observations	45	8	9	29	5	15	14
Mean value (g per 100 ml of serum)	7.4	6.3	6.5	6.3	6.1	6.2	6.5
Standard deviation for mean value	±1.20	±0.75	±0.49	±0.45	±0.99	±0.72	±0.58
Mean value (total amount, g)	216.2	277.2	271.8	265.1	232.8	234.2	274.9
Standard deviation for mean value	±38.31	±42.47	±36.30	±34.33	±34.25	±31.28	±49.74
Mean value (g per kg of body weight)	4.0	4.1	4.1	3.7	3.6	3.4	3.7
Standard deviation for mean value	±0.10	±0.66	±0.56	±0.79	±0.80	±0.64	±0.24

Table II. *Total Serum Protein (Statistical Significance of Differences (P))*

Weeks of Pregnancy	32–34	35–37	38–40
g per 100 ml of serum.			
Non-pregnant—pregnancy	<0.001	<0.001	<0.001
Normal pregnancy—pre-eclampsia	>0.05	>0.05	>0.05
Total circulating amount:			
Non-pregnant—pregnancy	<0.001	$0.01>P>0.001$	<0.001
Normal pregnancy—pre-eclampsia	>0.05	$0.05>P>0.01$	>0.05
g per kg of body weight			
Non-pregnant—pregnancy	>0.05	$0.05>P>0.01$	$0.05>P>0.01$
Normal pregnancy—pre-eclampsia	>0.05	$0.01>P>0.001$	>0.05

Table V *Serum α_1-Globulin (Relative Percentage g per 100 ml of Serum Total Circulating Amount Amount per kg of Body Weight)*

Weeks of Pregnancy	Non Pregnant	Normal Pregnancy			Pre-eclampsia		
		32 34	35–37	38–40	32 34	35–37	38–40
Number of observations	45	8	9	29	5	15	14
Mean value (relative percentage)	4.2	6.2	5.9	6.2	6.5	7.0	6.3
Standard deviation for mean value	±1.08	±0.80	±0.83	±0.42	±0.75	±0.65	±0.58
Mean value (g per 100 ml of serum)	0.3	0.4	0.4	0.4	0.4	0.4	0.4
Standard deviation for mean value	±0.09	±0.08	±0	±0.05	±0.06	±0.16	±0.13
Mean value (total amount, g)	8.7	17.1	16.0	15.9	14.9	16.2	17.6
Standard deviation for mean value	±2.68	±4.92	±3.58	±3.49	±3.04	±2.74	±3.59
Mean value (g per kg of body weight)	0.2	0.3	0.2	0.2	0.2	0.2	0.2
Standard deviation for mean value	±0.06	±0.07	±0.06	±0.06	±0.05	±0.05	±0.06

α_1-globulin, calculated per unit of serum, does not show any significant changes during pregnancy Nor is there any difference between the pre-eclamptic and normally pregnant group

The total amount of circulating α_1-globulin increases significantly in pregnant subjects as compared with *non-pregnant* women Between normally pregnant women and toxaemic subjects no statistically significant differences exist.

As regards the amount of circulating α_1-globulin calculated per kg of body weight there were no significant differences either between non-pregnant and pregnant women or between normal and toxaemic pregnancy

α_2-globulin. The results are summarised in Tables VII and VIII

Table IV *Serum Albumin (Statistical Significance of Differences (P))*

Weeks of Pregnancy	32–34	35–37	38–40
Relative percentage			
Non-pregnant—pregnancy	<0.001	<0.001	<0.001
Normal pregnancy—pre-eclampsia	>0.05	>0.05	>0.05
g per 100 ml of serum.			
Non-pregnant—pregnancy	<0 001	<0.001	<0.001
Normal pregnancy—pre-eclampsia	>0.05	>0 05	>0.05
Total circulating amount.			
Non-pregnant—pregnancy	>0.05	>0.05	0.05>P>0.01
Normal pregnancy—pre-eclampsia	>0.05	0.01>P>0 001	>0.05
g per kg of body weight			
Non-pregnant—pregnancy	0.01>P>0 001	<0.001	<0.001
Normal pregnancy—pre-eclampsia	>0.05	0.01>P>0.001	>0.05

ever is somewhat higher than in non pregnant subjects and in this period of gestation the difference is almost significant. The total amount of circulating albumin is lower in pre-eclamptic than in normal pregnancy but the difference is statistically significant only at the 35th–37th weeks

The amount of circulating albumin per kg of body weight differs significantly between pregnant and non pregnant subjects, the values being lower during pregnancy Except for the 35th–37th week period when a small but significant difference was found no differences exist between normal pregnant subjects and toxaemic women

α_1-globulin. The results are summarized in Tables V and VI The relative percentage of this fraction is higher during pregnancy and the differences are highly significant. No significant differences seem to exist between normally pregnant subjects and pre-eclamptic women although there is an almost significant difference between women at the 35th–37th week of gestation

Table VII. *Serum α_1-Globulin (Relative Percentage· g per 100 ml of Serum, Total Circulating Amount· Amount per kg of Body Weight)*

Weeks of Pregnancy	Non Pregnant	Normal Pregnancy			Pre-eclampsia		
		32 34	35–37	38–40	32 34	35–37	38–40
Number of observations	45	8	9	29	5	15	14
Mean value (relative percentage)	8.8	11.5	9.8	10.5	11.9	11.6	11 1
Standard deviation for mean value	± 2.32	± 1.24	± 0.84	± 1.72	± 2.03	± 1.65	± 1 46
Mean value (g per 100 ml of serum)	0.7	0.7	0 6	0.7	0.7	0.7	0.7
Standard deviation for mean value	± 0.19	± 0.08	± 0.11	± 0.12	± 0.09	± 0.13	± 0.14
Mean value (total amount, g)	18.7	32.5	26.0	27.9	26.6	27 4	30.8
Standard deviation for mean value	± 5.78	± 6 63	± 4.94	± 5.16	± 1.38	± 4.38	± 8.03
Mean value (g per kg of body weight)	0.3	0.5	0.4	0 4	0.4	0.4	0.4
Standard deviation for mean value	± 0 12	± 0.11	± 0.07	± 0.10	± 0 08	± 0.09	± 0.07

The total amount of circulating α_1-globulin calculated per kg of body weight does not exhibit any significant differences between the pregnant and non-pregnant states Nor is there any significant difference between toxaemic and normal pregnancy

β-globulin. The relative percentage of this protein fraction is found to be higher during pregnancy and the differences are highly significant (Tables IX and X) There are no differences between the levels in normal and pre-eclamptic pregnancies. Between the 38th–40th week of gestation, however the values obtained in toxaemic subjects are somewhat higher than during normal pregnancy but the difference is only almost significant.

The β-globulin fraction per unit of serum is significantly higher

Table VI. *Serum α -Globulin (Statistical Significance of Differences (P))*

Weeks of Pregnancy	32–34	35–37	38–40
Relative percentage:			
Non-pregnant—pregnancy	<0 001	<0.001	<0.001
Normal pregnancy—pre-eclampsia	>0.05	0.05>P>0.01	>0.05
g per 100 ml of serum.			
Non-pregnant—pregnancy	>0.05	>0.05	>0.05
Normal pregnancy—pre-eclampsia	>0.05	>0.05	>0.05
Total circulating amount:			
Non-pregnant—pregnancy	<0.001	<0.001	<0.001
Normal pregnancy—pre-eclampsia	>0 05	>0.05	>0.05
g per kg of body weight			
Non-pregnant—pregnancy	>0 05	>0.05	>0.05
Normal pregnancy—pre-eclampsia	>0.05	>0.05	>0.05

The relative percentage of this fraction increases during pregnancy and the differences between non-pregnant and pregnancy levels are highly significant. No significant differences were found between normal and pre-eclamptic pregnancies. The levels in the toxaemic group were found to be almost significantly higher than in the normally pregnant group only between the 35th–37th weeks.

The α_2-globulin fraction calculated per unit of serum does not differ during pregnancy Nor are there any differences between normal pregnant and pre-eclamptic subjects.

The toal amount of circulating α_2-globulin increases during pregnancy and highly significant differences were found between the non-pregnant and pregnant groups The total amount of this protein fraction shows no difference in toxaemia of pregnancy as compared with normal pregnancy

Table IX. Serum β-Globulin (Relative Percentage g per 100 ml of Serum Total Circulating Amount Amount per kg of Body Weight)

Weeks of Pregnancy	Non Pregnant	Normal Pregnancy			Pre-eclampsia		
		32 34	35–37	38–40	32–34	35–37	38–40
Number of observations	45	8	9	29	5	15	14
Mean value (relative percentage)	9.9	16.5	15.6	15.7	17.1	16.6	16.9
Standard deviation for mean value	±1.22	±2.86	±2.69	±1.86	±1.64	±2.87	±2.77
Mean value (g per 100 ml of serum)	0.7	1.0	1.0	1.0	1.0	1.0	1.1
Standard deviation for mean value	±0.07	±0.22	±0.09	±0.16	±0.06	±0.19	±0.24
Mean value (total amount, g)	21.3	45.4	42.6	41.9	38.6	38.5	47.1
Standard deviation for mean value	±3.96	±11.38	±10.99	±8.89	±3.48	±7.17	±13.00
Mean value (g per kg of body weight)	0.4	0.7	0.6	0.6	0.6	0.6	0.6
Standard deviation for mean value	±0.05	±0.19	±0.14	±0.13	±0	±0.15	±0.12

week) however the levels were found to be lower in pregnant than in non-pregnant women and the difference is highly significant

As regards the amount of γ-globulin per unit of serum the levels found during pregnancy are significantly lower than in non pregnant women. No differences exist between normal pregnant and pre-eclamptic subjects.

The total circulating amount of γ-globulin and the amount per kg of body weight do not differ either between non-pregnant and pregnant women or between normal pregnant and toxaemic subjects.

Table VIII. *Serum α_1-Globulin (Statistical Significance of Differences (P))*

Weeks of Pregnancy	32–34	35–37	38–40
Relative percentage			
Non-pregnant—pregnancy	<0.001	<0.001	<0.001
Normal pregnancy—pre-eclampsia	>0.05	0.05>P>0.01	>0.05
g per 100 ml of serum.			
Non-pregnant—pregnancy	>0.05	>0.05	>0.05
Normal pregnancy—pre-eclampsia	>0.05	>0.05	>0.05
Total circulating amount			
Non-pregnant—pregnancy	<0.001	<0.001	<0.001
Normal pregnancy—pre-eclampsia	>0.05	>0.05	>0.05
g per kg of body weight			
Non-pregnant—pregnancy	>0.05	>0.05	>0.05
Normal pregnancy—pre-eclampsia	>0.05	>0.05	>0.05

during pregnancy No significant differences exist between the levels in toxaemic and normal pregnancies.

The total amount of circulating β-globulin is increased significantly during pregnancy This fraction however displays considerable individual differences Therefore no constant trend as to differences between normally pregnant women and toxaemic subjects could be established.

As regards the β-globulin calculated per kg of body weight significantly higher values were found in the pregnant state No differences were found between normal pregnant and pre-eclamptic patients

γ-globulin The relative percentage of the γ-globulin fraction (Tables XI and XII) does not show any marked differences between non-pregnant and pregnant women between the 32nd–37th week of gestation In the last three-week period (38th–40th

Table XI. Serum γ-Globulin (*Relative Percentage: g per 100 ml of Serum, Total Circulating Amount: Amount per kg of Body Weight*)

Weeks of Pregnancy	Non Pregnant	Normal Pregnancy			Pre-eclampsia		
		32–34	35–37	38–40	32–34	35–37	38–40
Number of observations	45	8	9	29	5	15	14
Mean value (relative percentage)	15.3	13.2	13.6	12.5	13.5	13.9	12.8
Standard deviation for mean value	±3.34	±2.06	±1.98	±2.13	±2.18	±2.36	±2.25
Mean value (g per 100 ml of serum)	1.1	0.8	0.9	0.8	0.8	0.9	0.8
Standard deviation for mean value	±0.31	±0.18	±0.20	±0.18	±0.14	±0.17	±0.23
Mean value (total amount, g)	33.2	36.4	36.7	32.9	30.9	32.5	35.2
Standard deviation for mean value	±11.69	±8.85	±6.92	±7.58	±7.86	±5.31	±10.44
Mean value (g per kg of body weight)	0.6	0.5	0.6	0.5	0.5	0.5	0.5
Standard deviation for mean value	±0.16	±0.09	±0.07	±0.12	±0.05	±0.15	±0.13

Pre-eclampsia

Total serum protein. Mack (1960) summarizing the results of a study on 14 cases of pre-eclampsia reported that the decrease in concentration of total serum protein at term was two to three times greater than that found during normal pregnancy. *De Alvarez* and *Afonso* (1964) on the other hand, on the basis of serum protein analyses in 19 cases of severe and 34 cases of mild pre-eclampsia concluded that there was no difference in this respect between normal and toxaemic pregnancy. *Freis* and *Kenny* (1948) determined the total amount of circulating protein in normal pregnancy in mild and severe pre-eclampsia and in eclampsia. A tendency towards reduced levels in toxaemia of preg-

Table X. *Serum β-Globulin (Statistical Significance of Differences (P))*

Weeks of Pregnancy	32–34	35–37	38–40
Relative percentage:			
Non-pregnant—pregnancy	< 0.001	< 0.001	< 0.001
Normal pregnancy—pre-eclampsia	> 0.05	> 0.05	0.05 > P > 0.0
g per 100 ml of serum.			
Non-pregnant—pregnancy	< 0.001	< 0.001	< 0.001
Normal pregnancy—pre-eclampsia	> 0.05	> 0.05	> 0.05
Total circulating amount:			
Non-pregnant—pregnancy	< 0.001	< 0.001	< 0.001
Normal pregnancy—pre-eclampsia	0.05 > P > 0.01	> 0.05	0.05 > P > 0.01
g per kg of body weight:			
Non-pregnant—pregnancy	< 0.001	< 0.001	< 0.001
Normal pregnancy—pre-eclampsia	> 0.05	> 0.05	> 0.05

Discussion

Normal Pregnancy

It has been shown repeatedly that the concentration of the total serum protein decreases during normal pregnancy. A similar although sometimes more pronounced trend has also been found for the albumin fraction. The α_1- and γ-globulin fractions calculated per unit plasma remain constant during pregnancy whereas the α_1-globulin shows a modest increase per unit total serum protein. The α_2- and β-globulin fractions, show an increase during pregnancy with regard to both standards of reference (e.g., *Lagercrantz* 1945–1946, *Moore*, *Du Pan* and *Buxton* 1949, *Coryell et al.* 1950, *Mack* 1960, *Reboud et al.* 1963, *Hytten* and *Leitch* 1964). The results of the present investigation are in principle in agreement with these earlier findings.

arrived at the same conclusion and claimed that in mild cases of toxaemia there was a statistically significant decrease in the relative concentration of serum albumin whereas in the severe cases there was a decrease both in absolute and relative concentration. In contrast to these investigators we have not been able to discern any statistically significant differences between normal pregnant subjects and toxaemic patients with respect to absolute and relative concentrations of serum albumin. On the other hand, we have observed a decrease of the total amount of circulating serum albumin in patients suffering from pre-eclampsia. Only for the 35th–37th week group however was there a statistically significant difference This was also the case when the serum albumin was related to body weight.

Serum globulins. Certain differences of opinion exist as to the occurrence of changes in this heterogeneous group of serum constituents in association with pre-eclampsia. *Mack* (1960) reported an increase of α_1- and α_2-globulins in this clinical condition irrespective of its degree of severity *De Alvarez* and *Afonso* (1964) found no such change in mild cases but reported that the absolute concentrations of α_1- and α_2-globulin and the relative concentration of α_2-globulin were significantly higher in patients suffering from a severe degree of pre-eclampsia than in a normal control group *Lagercrantz* (1945–1946) found a slight and not statistically significant decrease of the β-globulin fraction in pre-eclamptic patients. *Mack* (1960) also noticed such a trend whereas *de Alvarez* and *Afonso* (1964) recorded a statistically significant increase in the absolute as well as relative concentration of β-globulin in this clinical condition As regards γ-globulin *Mack* (1960) found a decrease in pre-eclampsia. This finding, however does not seem to have been confirmed. The present authors found no statistically significant differences between pre-eclampsia and normal pregnancy with respect to any of the globulin fractions.

De Alvarez and *Afonso* (1964) concluded that, on theoretical grounds, the determination of the different serum protein fractions would be of importance for the diagnosis of toxaemia In practice however these investigators were not able to confirm this opinion *Bronsema* (1965) also studied the protein spectrum

Table XII. *Serum γ-Globulin (Statistical Significance of Differences (P))*

Weeks of Pregnancy	32–34	35–37	38–40
Relative percentage			
Non-pregnant—pregnancy	>0.05	>0.05	<0.001
Normal pregnancy—pre-eclampsia	>0.05	>0.05	>0.05
g per 100 ml of serum.			
Non pregnant—pregnancy	<0.001	<0 001	<0 001
Normal pregnancy—pre-eclampsia	>0 05	>0.05	>0.05
Total circulating amount			
Non-pregnant—pregnancy	>0 05	>0.05	>0 05
Normal pregnancy—pre-eclampsia	>0 05	>0.05	>0 05
g per kg of body weight			
Non-pregnant—pregnancy	>0.05	>0.05	>0.05
Normal pregnancy—pre-eclampsia	>0.05	>0.05	>0.05

nancy was found varying between 1 9 to 3 0 g per kg of body weight (mean value 2.2 g) as compared with 3 6 g per kg of body weight during normal pregnancy Considerable individual variations and overlap of values between the different groups were observed, however In the present study statistically significant differences were found only in toxaemic subjects of the 35th–37th week group *i.e* in patients with early manifestations of the disease and furthermore only when the total circulating serum protein was related to body weight. All other differences were of no statistical significance

Serum albumin. Scrimshaw and *Alling* (1949) in 46 of 52 cases with mild and severe pre-eclampsia found a tendency towards low levels of albumin in comparison with normal pregnancy In some cases a decrease of the albumin fraction preceded the clinical manifestations of the disease However no quantitative data were reported. *De Alvarez* and *Afonso* (1964) in principle

tistically significant differences of the various protein fractions have been recorded in cases of pre-eclampsia as compared with normal pregnancy at the same periods of gestation.

REFERENCES

Bonnier G. and Tedin O. Biologisk variationsanalys, Stockholm 1940

Brody S. and Spetz S. Acta obst. et gynec. scand. 46 138, 1967

Bronsema A. Pregnancy Chemistry and Management. American Lecture Series 1965

Coryell M. N. Beach, E. F. Robinson A. R., Macy I. G. and *Mack, H. C.*, J. clin. Invest. 29 1559 1950

de Alvarez R. R. and *Afonso J. F.* Amer J. Obstet. Gynec. 88 774 1964

Freis E. D. and *Kenny J. F.* J. clin. Invest. 27 283, 1948

Hytten F. E. and *Leitch, I.* The Physiology of Human Pregnancy Blackwell Scientific Publications, Oxford, 1964

Lagercrantz C. Upsala läkareförening. Förhandlingar 51 117 1945–1946

Lang, K. und *Lehnartz E.*, Handbuch der Physiologisch- und Pathologisch-chemischen Analyse Berlin–Göttingen–Heidelberg, 1953

Lehmann J. Nordisk Medicin 21 317 1944

Mack, H. C., Clin. obst. gynec. 3 336, 1960

Moore D. H. Du Pan R. M., and Buxton C. L., Amer J. Obstet. Gynec. 57 312, 1949

Reboud P. Groulade J. Groslambert P. and Colomb M. Amer J. Obstet. Gynec. 86 820 1963

Scribnshaw N. S. and *Alling, E. L.*, Fed. Proc. 8 368, 1949

Received on Sept. 2nd, 1968

in 13 patients with toxaemia of pregnancy in the third trimester Differences from the normal pattern were observed, significant changes being recorded only in patients with albuminuria On the other hand serious cases with grave symptoms of toxaemia did not invariably exhibit an abnormal pattern of the protein spectrum.

In the present study no consistent changes in the different protein fractions were found in pre-eclamptic patients as compared with the conditions observed during normal pregnancy The data presented here do not enable us to support the view that the assessment of the protein spectrum is of importance, for the diagnosis or treatment of the disease. Although definite alterations of the protein spectrum were seen in some cases no pathognomonic and significant changes could be observed.

SUMMARY

The total serum protein and its different fractions have been studied in 34 patients with mild and severe pre-eclampsia. As controls 45 non-pregnant women and 46 normal pregnant subjects have been studied.

The amounts per unit of serum, the relative percentages of the different fractions the total circulating amounts and the amounts per unit of body weight have been calculated. Statistical analysis of the results have been carried out.

In comparison with non-pregnant controls significant changes in total serum protein, albumin α_1- α_2- β- and γ-globulin have been found during pregnancy

In comparison with conditions obtaining during normal pregnancy the total amount of serum protein per kg of body weight is significantly lower in cases of toxaemia between the 35th–37th week of gestation

Between the 35th–37th weeks the total amount of circulating albumin and the amount per kg of body weight have also been found to be significantly lower in cases of pre-eclampsia in comparison with normal pregnancy

With the exception of the above-mentioned findings no sta-

Table I. Maternal Mortality and Proportion Due to Rupture of Uterus in Swedish Departments of Obstetrics (Partly According to Bjerre 1958 and Bjerre and Arendt 1964)

Period	1930–1935	1950–1955	1956–1961
Deliveries	82,403	343,182	407,340
Maternal deaths	245	177	110
Maternal deaths per 100,000 deliveries	293	52	27
Maternal deaths due to rupture of uterus	10	11	15
Maternal deaths due to rupture of uterus per 100,000 deliveries	12.1	3.2	3.7
Deaths from rupture of uterus as per cent of maternal deaths	4.8	6.2	13.6

Four died from postoperative complications.

Table II. Causes of Rupture of Uterus 1955–1961 (Department of Obstetrics)

Cause	Number
Traumatic	24 (10)
Scar after Caesarean section or hysterotomy	18 (1)
Other mural injuries	19 (1)
Obstruction	14 (2)
Miscellaneous	8 (1)
Total	83 (15)

() Maternal deaths.

pare this incidence with that in published series because the latter are usually small. Any large series date back to before the advent of antibiotics and before the development of modern transfusion techniques.—In U.S.A. the frequency in series collected after 1945 is about 1 : 2000 (*Eastman* 1956) 1 : 3089 (*Ervring*, 1957) 1 : 2086 (*Waters* and *Hall* 1962). *Turunen* (1959) found a frequency of 1 : 3249 in a clinical series covering the period 1944–1957

From the Department of Obstetrics and Gynaecology (T Wahlén MD)
General Hospital Hälsingborg, Sweden

RUPTURE OF THE UTERUS IN SWEDISH DEPARTMENTS OF OBSTETRICS 1956—1961

BY

BIRGER ÅSTEDT

In a recent investigation of the maternal mortality in Swedish departments of obstetrics (*Bjerre* and *Astedt* 1964) the mortality rate during 1956–1961 was found to be lower than in previous periods But of the 110 deaths that occurred during that period, 15 (13 6 per cent) were due to rupture of the uterus. The proportion of maternal deaths due to rupture of the uterus shows an increase when compared with the 6-year periods 1930–1935 (4.8 per cent) and 1950–1955 (6 2 per cent) (Table I) It was therefore thought that analysis of all cases of uterine rupture occurring in departments of obstetrics during the period 1956–1961 might reveal ways for improvement of the prophylaxis diagnosis and treatment of the condition.

Material and Methods

The clinical material consisted of all cases of rupture of the uterus at Swedish departments of obstetrics during the period 1956–1961 The hospital records and the pathologists reports at all hospitals were studied Dubious cases were discussed with the chiefs of the respective departments.

Results and Discussion

Frequency Uterine rupture occurred in only 83 out of 407,340 deliveries, *i e* 1 4908 a fairly small figure It is difficult to com-

10 maternal deaths occurred in this group an incidence of 42 per cent. The foetal mortality of 75 per cent, was also high.

This group included 2 cases in which large ruptures occurred during Caesarean section which made hysterectomy necessary In one case the child was large and in one version was performed through the incision in the uterus before the child was extracted.

Rupture in association with fundal expression of the child has been reported (*Ferguson* and *Reid*, 1958 *Pedovitz* and *Perell* 1958) In a series of 84 ruptures *Ferguson* and *Reid* (1958) found 3 cases associated with suprafundal pressure and they draw attention to the risk of this operation.—In the case given in Table IV the woman had a history of 2 abortions followed by curettage Histological examination showed the musculature at the site of the rupture to be unusually rich in connective tissue, so that injury of the wall was probably a contributory cause.

High and midforceps deliveries and version and extraction were the commonest causes of traumatic rupture (Table IV) While the frequency of Caesarean section has remained fairly constant, instrumental delivery has increased in frequency in recent years, probably because of the introduction of the vacuum extractor which is used for a wide range of indications (*Lundgren* and *Asted*t 1963) Probably because of this change in policy only one of the 12 ruptures in association with forceps delivery occurred during the last 2 years of the 1956–1961 period.—The vacuum extractor was used in some of the 83 cases, but in none was there reason to suppose that it was the cause of the rupture

Rupture during expression of the placenta is rare and occurred in only one case. The rupture in that case was incomplete.

In the evaluation of traumatic ruptures it must, however be borne in mind that the rupture may have occurred earlier but remained concealed until operation was indicated because of for example poor foetal heart sounds bleeding or cessation of contractions. In 2 cases the operation was performed because of threatened uterine rupture and the rupture would probably have occurred even if the operation had not been performed.

Spontaneous rupture after previous Caesarean section or hysterotomy 18 (22 per cent) of the 83 ruptures occurred after

Table III. *Rupture of Uterus in Departments of Obstetrics in 1955-1961 Grouped According to Parity and Age of Mothers*

Parity	< 20 Years	20-29	30-39	40	Total
Para 0	0	1	4	0	5
Para I-IV	1	20	34 (7)	12 (6)	67 (13)
Para V	0	1	7 (1)	3 (1)	11 (2)
Total	1	22	45 (8)	15 (7)	83 (15)

() Maternal deaths.

The distribution of rupture of the uterus according to main causes patients age and previous deliveries is given in Tables II and III

Maternal mortality 15 (18 per cent) of the 83 ruptures were fatal including 4 deaths from postoperative complications (3 from postoperative ileus and one from supervening thrombosis of the carotid artery in a diabetic) *Turunen* (1959) found the mortality from ruptured uterus to be 13.3 per cent. The total maternal mortality during the period was 110 (*Bjerre* and *Astedt* 1964) and rupture of the uterus was responsible for 13 6 per cent which is a higher proportion than that in the 2 previous 6-year periods (Table I)

Foetal mortality 56 (68 per cent) of the 83 foetuses died, but in 8 cases rupture was not the direct cause of death. There were no twin pregnancies In *Turunen s* (1959) series the foetal mor tality was 40 per cent Of the 15 cases in which the mother died, 2 of the children survived

Traumatic ruptures constitute the largest and most important part of the series especially because of the high mortality they claim. 24 (29 per cent) of the 83 ruptures were traumatic *Pär nänen* (1949) reported 16 5 per cent, *Turunen* (1959) 25 per cent and *Ferguson* and *Reid* (1958) only 11 per cent, probably because of the wider range of indications for Caesarean section in U.S.A

In 2 cases the patients had had an uncomplicated delivery between the time of the Caesarean section and the delivery that led to rupture. This shows that a scar may tolerate the strain of one normal delivery but not necessarily of a subsequent one. It is well known that the frequency of rupture is higher in multiparae because of successive weakening of the musculature. The scar tissue probably becomes still weaker from one pregnancy to the next with consequent increase in the risk of rupture.

Only one maternal death occurred in this group The woman had diabetes with nephropathy and the postoperative course was complicated by thrombosis of the left carotid artery The low mortality rate is remarkable However bleeding was less profuse in these cases because of the relative avascularity of the tissue at the site of rupture (*Josey* 1963) and severe shock rarely occurred, in contrast to the findings in the traumatic group

Very weak and avascular scar tissue is not uncommonly observed at repeat Caesarean section when it may be seen to be almost as thin as paper This was illustrated in one of the cases. Repeat Caesarean section revealed a defect twice the breadth of a finger in the old scar which had produced no symptoms. A similar illustrative example is described below

A 32 year old Para-V delivered on the last occasion by classical Caesarean section because of placenta praevia. The patient was now pregnant again and was admitted one month before calculated term because of 3 days pain in the right side of the abdomen. Uterine contractions had not started She was in good general condition and afebrile. Just below the right costal margin there was a first-sized lump extremely tender to palpation and below this in the right flank a similar tender lump the size of a hen egg. Otherwise the abdomen was not tender and there were no signs of peritonitis. At the time of the previous Caesarean section the patient had been informed that she had myomas and now necrosis of the myoma or torsion of an ovarian cyst was suspected

Laparotomy was decided upon and a muscle-splitting incision was made over the palpated masses On opening the peritoneum a foot was revealed and therefore a midline incision was made. The old uterine scar was ruptured and half of the foetus projected into the abdominal cavity The child was readily lifted out and survived. There was no blood or liquor amnii in the abdomen The uterus was removed. The remarkable thing about this case is that there were hardly any symptoms and that no bleeding had occurred despite the large rupture, with half of the foetus extruded into the abdominal

Table IV *Causes of Traumatic Rupture*

Operative Procedure	Numbers of Ruptures (Deaths Included)	Maternal Deaths
Caesarean section	2	0
Suprafundic pressure to deliver the child	1	0
Version and extraction	6	2
Craniotomy	1	1
High forceps and craniotomy	1	1
High and mid forceps	11	4
Low forceps with occipito-posterior presentation	1	1
Expression of placenta	1	1
Total	24	10

Contributory cause: Toxaemia.

previous incision of the uterus Of 15 Caesarean sections 11 were classical the others were transverse incisions in the lower uterine segment. This shows that attempts to eliminate the risk of rupture after Caesarean section by using a low transverse incision in the least contractile segment of the uterus (*Hedberg*, 1943) was not so successful as had been hoped. Three cases of rupture in scars after hysterotomy for legal abortion were included in this group one after a transverse incision in the fundus and two after a longitudinal incision

Oxytocic drugs were given by intravenous infusion in 6 patients with uterine scars. Three had a previous transverse incision and 3 had a longitudinal incision In all of these cases the drug was probably a contributory cause to the rupture The risk of giving such drugs to women who have previously been delivered by Caesarean section has been stressed by *Ferguson* and *Reid* (1958) among others

It has been claimed that the risk of rupture is greater when the placenta is attached at the site of the scar (*Arfwedson* 1952 *Wilson* 1951) In 5 of our patients the placenta was *known to* occupy this position In these cases bleeding was very profuse

In 2 cases the patients had had an uncomplicated delivery between the time of the Caesarean section and the delivery that led to rupture. This shows that a scar may tolerate the strain of one normal delivery but not necessarily of a subsequent one. It is well known that the frequency of rupture is higher in multiparae because of successive weakening of the musculature. The scar tissue probably becomes still weaker from one pregnancy to the next with consequent increase in the risk of rupture

Only one maternal death occurred in this group The woman had diabetes with nephropathy and the postoperative course was complicated by thrombosis of the left carotid artery The low mortality rate is remarkable. However bleeding was less profuse in these cases because of the relative avascularity of the tissue at the site of rupture (*Josey* 1963) and severe shock rarely occurred, in contrast to the findings in the traumatic group

Very weak and avascular scar tissue is not uncommonly observed at repeat Caesarean section when it may be seen to be almost as thin as paper This was illustrated in one of the cases Repeat Caesarean section revealed a defect twice the breadth of a finger in the old scar which had produced no symptoms. A similar illustrative example is described below

A 32 year old Para-V delivered on the last occasion by classical Caesarean section because of placenta praevia. The patient was now pregnant again and was admitted one month before calculated term because of 3 *days* pain in the right side of the abdomen. Uterine contractions had not started. She was in good general condition and afebrile. Just below the right costal margin there was first-sized lump extremely tender to palpation and below this in the right flank similar tender lump the size of hen s egg Otherwise the abdomen was not tender and there were no signs of peritonitis. At the time of the previous Caesarean section the patient had been informed that she had myoma and now necrosis of the myoma or torsion of an ovarian cyst was suspected.

Laparotomy was decided upon and a muscle-splitting incision was made over the palpated masses On opening the peritoneum a foot was revealed and therefore a midline incision was made. The old uterine scar was ruptured and half of the foetus projected into the abdominal cavity The child was readily lifted out and survived. There was no blood or liquor amnii in the abdomen The uterus was removed. The remarkable thing about this case is that there were hardly any symptoms and that no bleeding had occurred despite the large rupture with half of the foetus extruded into the abdominal

Table IV *Causes of Traumatic Rupture*

Operative Procedure	Numbers of Ruptures (Deaths Included)	Maternal Deaths
Caesarean section	2	0
Suprafundic pressure to deliver the child	1	0
Version and extraction	6	2
Craniotomy	1	1
High forceps and craniotomy	1	1
High and mid forceps	11	4
Low forceps with occipito-posterior presentation	1	1
Expression of placenta	1	1
Total	24	10

Contributory cause: Toxaemia.

previous incision of the uterus Of 15 Caesarean sections 11 were classical the others were transverse incisions in the lower uterine segment. This shows that attempts to elminiate the risk of rupture after Caesarean section by using a low transverse incision in the least contractile segment of the uterus (*Hedberg*, 1943) was not so successful as had been hoped. Three cases of rupture in scars after hysterotomy for legal abortion were included in this group one after a transverse incision in the fundus and two after a longitudinal incision

Oxytocic drugs were given by intravenous infusion in 6 patients with uterine scars Three had a previous transverse incision and 3 had a longitudinal incision In all of these cases the drug was probably a contributory cause to the rupture The risk of giving such drugs to women who have previously been delivered by Caesarean section has been stressed by *Ferguson* and *Reid* (1958) among others

It has been claimed that the risk of rupture is greater when the placenta is attached at the site of the scar (*Arfwedson* 1952 *Wilson* 1951) In 5 of our patients the placenta was known to occupy this position. In these cases bleeding was very profuse

In 2 cases the patients had had an uncomplicated delivery between the time of the Caesarean section and the delivery that led to rupture. This shows that a scar may tolerate the strain of one normal delivery but not necessarily of a subsequent one. It is well known that the frequency of rupture is higher in multiparae because of successive weakening of the musculature The scar tissue probably becomes still weaker from one pregnancy to the next with consequent increase in the risk of rupture.

Only one maternal death occurred in this group The woman had diabetes with nephropathy and the postoperative course was complicated by thrombosis of the left carotid artery The low mortality rate is remarkable However bleeding was less profuse in these cases because of the relative avascularity of the tissue at the site of rupture (*Josey* 1963) and severe shock rarely occurred in contrast to the findings in the traumatic group

Very weak and avascular scar tissue is not uncommonly observed at repeat Caesarean section when it may be seen to be almost as thin as paper This was illustrated in one of the cases Repeat Caesarean section revealed a defect twice the breadth of a finger in the old scar which had produced no symptoms. A similar illustrative example is described below

A 32-year old Para-V delivered on the last occasion by classical Caesarean section because of placenta praevia. The patient was now pregnant again and was admitted one month before calculated term because of 3 days pain in the right side of the abdomen. Uterine contractions had not started. She was in good general condition and afebrile. Just below the right costal margin there was fist-sized lump extremely tender to palpation and below this in the right flank similar tender lump the size of hen s egg. Otherwise the abdomen was not tender and there were no signs of peritonitis. At the time of the previous Caesarean section the patient had been informed that she had myoma and now necrosis of the myoma or torsion of an ovarian cyst was suspected

Laparotomy was decided upon and muscle-splitting incision was made over the palpated masses On opening the peritoneum foot was revealed and therefore midline incision was made. The old uterine scar was ruptured and half of the foetus projected into the abdominal cavity The child was readily lifted out and survived. There was no blood or liquor amnii in the abdomen The uterus was removed. The remarkable thing about this case is that there were hardly any symptoms and that no bleeding had occurred despite the large rupture with half of the foetus extruded into the abdominal

cavity The liquor had probably been resorbed in the abdominal cavity during the 3 days since the onset of symptoms.

Other injuries of the uterine wall This group which comprised of 19 (17 per cent) of the 83 ruptures was difficult to classify and some of the cases could also have been assigned to the group with unknown causes

Of 11 cases with certain injury to the wall rupture was associated with myoma in 2 cases In one rupture occurred at the site of a cervical myoma—which was hardly large enough to obstruct delivery and in the other rupture was in the scar tissue after enucleation of a myoma In the other 9 cases histological examination showed fibrosis in the area of the rupture These women had a history of difficult delivery curettage abortions followed by curettage or infections which could probably explain the fibrosis. *Levi* (1961) found that rupture after enucleation of a myoma is rare and therefore felt that there is no reason to refrain from such conservative treatment. Of 215 published cases of rupture in women with tumour endometriosis or a mole *Englund* and *Odeblad* (1950) found only 17 to be due to previous enucleation of a myoma. This is a fairly low figure in view of the frequency with which this operation is performed.

Of 8 patients hesitantly assigned to this group 6 had had at least one evacuation after abortion plus in some instances a history of curettage for other reasons The significance of abortion has often been discussed and the role it played in these cases is obscure But no other probable cause could be found. Of the remaining 2 patients one a 40-year old woman had had 9 normal deliveries illustrating the old experience that advancing age and increasing parity weaken the muscle of the uterus In the other case there were unusually large venous vascular formations in the uterine wall and a small peritoneal rupture caused profuse bleeding

Only one maternal death occurred in this group

Obstructed labour 14 of the 83 ruptures were due to obstructed labour

A narrow pelvis was the cause in two cases In one of them

radiological pelvimetry was misleading and oxytocin was given by intravenous infusion In the other case the pelvis was also narrower than was suggested by roentgen examination and at a previous delivery craniotomy had been performed.

Hydrocephalus occurred in one case and was not discovered until delivery The child presented by the breech and the head was extracted by the method of Mauriceau-Smellie-Veit combined with forceful pressure on the uterus. It is possible that this caused rupture and this case should thus perhaps be assigned to the traumatic group

Rigidity of the cervix was the cause of rupture in one case. Utedrin was given by intravenous infusion and might have been a contributory cause.

Abnormal presentations were as follows Transverse and oblique in 2, brow in 2, face in 1 high midposition in 2, asynclitism in 1 and occipitoposterior in 2. Oxytocin was given in the 2 last mentioned cases. The vacuum extractor was used in one case with abnormal presentation and in another cranioclasia was carried out. In both of them rupture certainly occurred before the operation. In the other cases laparotomy was performed without any preceding intervention

Two mothers in this group died. The foetal mortality was high, namely 85 7 per cent.

Other causes. In 8 of the 83 cases the cause of rupture was uncertain. Labour-inducing drugs resulting in very intense and frequent contractions were given to 4 of these women, including one patient who had had 5 normal deliveries.

Of the remaining 4 cases the last delivery in one, a Para-III was difficult and might have caused injury to the wall. No other observations of interest had been made in these cases.

Diagnosis. In the discussion of the diagnosis it may appear unwarranted to classify the cases according to their aetiology The traumatic ruptures and ruptures of scars after previous Caesarean section, however occupy a special position and will be discussed separately

In 6 of the 24 cases of *traumatic rupture* shock occurred immediately after the operation and pointed to the diagnosis. In

most cases shock was profound and though rupture was suspected immediately 2 of the patients died.

Routine inspection and exploration led to the diagnosis in 7 cases Two of the women died but from postoperative complications

In 8 patients exploration was not done until bleeding had occurred and shock was impending In all of them the shock became profound and 6 of them died Four of the cases (all fatal) in which the diagnosis was delayed further because the rupture was not detected at the first exploration are instructive In 3 of them this was probably because the bleeding was believed to be due solely to placental retention and the uterus was explored without any special search for rupture

The importance of careful routine exploration of the uterine cavity after difficult delivery has been stressed by several authors (*Bak* and *Hayden* 1955 *Pedowitz* and *Perell* 1959 *Boulle* and *Crichton* 1964) If the diagnosis is not established before signs of shock appear the prognosis is much worse as shown by the above cases

In 3 cases the diagnosis was only established during the puerperium. These cases are discussed in a later section

In *ruptures of scars after previous Caesarean section* the examiners were naturally more observant, and in practically all of them the diagnosis was established early

In 5 of the 18 cases the rupture was diagnosed before labour had started. Marked tenderness led to the diagnosis in 2 cases, repeat section in 2 and in the remaining case exploratory laparotomy one month before term In the latter case it was known that the patient had a uterine myoma and the preoperative diagnosis was necrosis of the myoma

In 12 cases there was pain and tenderness on palpation over the uterus during labour and in all of them the foetal heart sounds were weak or absent and these findings together led to the diagnosis In 3 of these women foetal parts were also palpated in the abdomen

In one case the diagnosis was made four days after parturition This case is discussed in a later section

Pain and tenderness on palpation of the uterus were thus the

Table V *Rupture of Uterus Diagnosed in Puerperium (8 Cases)*

Cause	Symptoms at Delivery	Bleeding at Delivery	Days between Delivery and Diagnosis	Symptoms in Puerperium	Preop. Diagnosis	Findings at Laparotomy
Forceps delivery	Poor foetal heart sounds Child dead	100 ml	2 days	Meteorism tenderness. Abd. X-ray: Ileus	Rupture	Complet rupture Little blood loss
Forceps delivery	Poor foetal heart sounds. Child dead	350 ml	2 days	Stabbing pain, respiratory distress meteorism	Rupture	Complet rupture. Abundant blood-stained fluid
Forceps delivery	Poor irregular foetal heart sounds. Child dead	375 ml	1 day	Meteorism. Signs of peritonitis	Uterine exploration. Rupture	Complet rupture Moderate amount of blood
Scar after Caesarean section	Tenderness over uterus	1000 ml	4 days	Tenderness over rt. *iliac fossa*	Appendicitis?	Incomplete rupture. Haematoma in rt. parametrium
Scar after Caesarean section	None	100 ml	2 days	Ileus	Rupture	Incomplete rupture. Vessel in uterin wall. 1 litre of blood
Scar after curettage	None	600 ml	16 days	Fever Stabbing pain, signs of peritonitis	Exploratory laparotomy	Peritonitis. Pus in abdomen
Obstruction	Dizziness, nausea, vomiting. Child dead	600 ml	3 days	Abdominal pain. Vaginal bleeding	Uterine exploration: rupture	Incomplete rupture. No blood in abdomen
Obesure	None	350 ml	1 day	Signs of ileus	Uterine exploration. rupture	Incomplete rupture. No blood in abdomen

dominating symptoms in combination with faint or inaudible foetal sounds It has been stressed that pain and tenderness on palpation are more severe in ruptures of scars after corporeal incisions where the peritoneum is distended, in contrast to that which is seen in low incisions where the peritoneum is more elastic (*Badau ay* 1960) No such difference was found in our cases

Cessation of labour was striking only in those cases where foetal parts could be palpated in the abdomen

In none of the cases was there any appreciable vaginal bleeding

In the 41 cases (other injuries to the wall 19 obstruction 14 others 8) where Caesarean section had not previously been done and where the women had not been operated upon before the diagnosis was often very problematic The condition most often suspected was premature detachment of the placenta.

Pain tenderness on palpation restlessness and faint or inaudible foetal sounds were the dominating symptoms in 25 cases and in 6 of them they were so severe that laparotomy was performed immediately In the other 19 cases foetal parts were palpated in the abdominal cavity and confirmed the diagnosis which was already suspected in most of the cases. In the event of rupture the presenting part of the foetus will slip upwards and this argues strongly for rupture This occurred in 4 of the cases

In 8 cases in which the women were delivered of stillborn infants and in which pain and tenderness to palpation were less severe the diagnosis was established at exploration of the uterine cavity in 6 and by exploratory laparotomy in one In one case with a narrow pelvis, uterine rupture that had produced no symptoms was detected at Caesarean section

Three cases, including one that was delivered spontaneously and 2 easily by low vacuum extraction are instructive and underline the importance of careful observation of the patient after parturition. The foetal heart sounds were slow and irregular but otherwise nothing suggested rupture For 10 minutes to 1 hour after parturition during which the patients had felt well signs of impending shock appeared After the onset of the first symptoms the women rapidly went into profound and irreversible shock. All 3 women died before adequate treatment could be given

Profuse vaginal bleeding occurred in 9 cases.

In 4 cases the diagnosis was not made until the puerperium.

Rupture of the uterus diagnosed in the puerperium. In 8 (9.6 per cent) of the 83 cases the diagnosis was made 1–16 days after parturition. In half of the cases the rupture was incomplete. The main symptoms were abdominal pain and meteorism. Stabbing pain has been described as a characteristic symptom (*Beacham* 1951 *Wachsman* 1953 *Pedowitz* and *Perell* 1958 *Weström* 1960) This occurred in only 2 of the cases.

The cases are summarized in Table V

No maternal deaths occurred.

Site of rupture In the 18 cases where Caesarean section had been performed previously the rupture occurred in the scar In 2 of them—both after a low transverse incision— the rupture had not extended through the peritoneum.

Of the remaining 65 cases the rupture was incomplete without perforation of the peritoneum, in 11 (17 per cent) In another case the rupture was incomplete but there was a rift in the peritoneum and a plexus of veins in the uterine wall.

The incomplete ruptures were strangely enough, all situated to the left and the haematomas had dissected their way out into the left parametrium. The haematomas were often fairly large and one of them extended up to the left kidney

In the cases of complete rupture the amount of blood in the abdomen was often between 0.5 and a few litres.

The sites of the ruptures—with the exception of women who had previously been delivered by Caesarean section—are given in Table VI *Boulle* and *Chrichton* (1964) reported a similar distribution.

Treatment Shock was treated in the conventional way and will not be discussed here. It should however be stressed that in many of the cases bleeding was profuse. Ten of the patients received more than 9 bottles (450 ml per bottle) of blood and even this was not always sufficient. In 2 cases treated successfully the women were given 27 and 33 bottles of blood It was often difficult to procure sufficient blood in time In some cases the in-

Table VI. *Site of Rupture*

Anterior	22 (4)
Posterior	6
Left lateral wall	24 (8)
Right lateral wall	12
Fundus	1
With associated rupture of bladder	2

() Incomplete ruptures included in the total numbers are given in brackets.

fusion was given without cross matching and the time thereby gained was certainly life-saving

Laparotomy was done in all cases except 5 in which the patients died before operation was possible. Packing of the uterine cavity was tried in one case but without effect on the bleeding Laparotomy was therefore done in this case, too

Total or subtotal hysterectomy was performed in 56 cases (68 per cent) The rupture was sutured in 22 cases (27 per cent) *Peretz* and *Grünstein* (1962) reported repair of the uterus in 24 per cent, *Pärnänen* (1949) 30.2 per cent and *Turunen* (1959) 38.9 per cent of cases

According to *Bak* and *Hayden* (1955) subtotal hysterectomy is the quickest way to control the bleeding This is however not always the case In the present series suture of the rupture was often undertaken because it is so easy to perform and so easily controls bleeding

Repair has also been regarded as carrying a greater risk of infection and therefore hysterectomy should be preferable But this risk has been markedly reduced by the availability of antibiotics. In the present series no difference was found between the two methods regarding the frequency of infection and postoperative ileus

Judging from the present investigation both methods are equally effective, but suture is usually preferable because it preserves the patient s fertility

SUMMARY

The frequency of rupture of the uterus in Swedish departments of obstetrics was studied during the 1956–1961 period. The proportion of maternal deaths due to uterine rupture has increased, as compared with the 1930–1935 and 1950–1955 periods In 407,340 deliveries rupture occurred in 83 with 15 (18 per cent) maternal deaths. The maternal mortality was much lower during the last 2 years with only one death in each. The foetal mortality was 68 per cent.

The 24 *traumatic ruptures* represented the largest and most important group often with profuse bleeding and profound shock and with a maternal mortality of 42 per cent. During the last 2 years the number of ruptures in association with forceps delivery was much lower probably because of the wider use of the vacuum extractor Careful routine examination of the uterus after difficult deliveries is necessary Postponement of such examination until after symptoms of shock have appeared impairs the prognosis considerably

Of the 18 cases with a history of Caesarean section or hysterotomy the previous incision was corporeal in 13 and transverse in 5 including one with incision of the fundus The blood loss was often slight because of the relative avascularity of the scar In most cases the symptoms were mild and atypical. In 5 cases no contractions occurred. The commonest symptom in the other cases was tenderness over the old scar Because of the history of previous Caesarean section in these cases the examiners were on the alert for the possibility of rupture The prognosis was favourable Only one maternal death occurred and was due to postoperative complications.

Nineteen ruptures occurred after other injuries to the wall, 14 owing to obstruction and in 8 cases the cause is obscure

In 8 (10 per cent) cases the diagnosis was only established during the puerperium. In these the main symptoms were abdominal pain and meteorism. Stabbing pain which is regarded as a characteristic symptom, occurred in only 2 cases.

The commonest sites for the ruptures—with the exception of women who had previously been delivered by Caesarean sec

Table VI. *Site of Rupture*

Anterior	22 (4)
Posterior	6
Left lateral wall	24 (8)
Right lateral wall	12
Fundus	1
With associated rupture of bladder	2

() Incomplete ruptures included in the total numbers are given in brackets.

fusion was given without cross matching and the time thereby gained was certainly life-saving.

Laparotomy was done in all cases except 5 in which the patients died before operation was possible. Packing of the uterine cavity was tried in one case but without effect on the bleeding Laparotomy was therefore done in this case too

Total or subtotal hysterectomy was performed in 56 cases (68 per cent) The rupture was sutured in 22 cases (27 per cent) *Peretz* and *Grünstein* (1962) reported repair of the uterus in 24 per cent *Pärnänen* (1949) 30.2 per cent and *Turunen* (1959) 38 9 per cent of cases

According to *Bak* and *Hayden* (1955) subtotal hysterectomy is the quickest way to control the bleeding This is however not always the case In the present series suture of the rupture was often undertaken because it is so easy to perform and so easily controls bleeding

Repair has also been regarded as carrying a greater risk of infection and therefore hysterectomy should be preferable But this risk has been markedly reduced by the availability of antibiotics. In the present series no difference was found between the two methods regarding the frequency of infection and postoperative ileus

Judging from the present investigation both methods are equally effective but suture is usually preferable because it preserves the patient s fertility

Jacobson, L., Kau, L. and Nilsson, A., Acta obst. et gynec. scandinav. 46, 183, 1967
From the Department of Obstetrics and Gynaecology (Professor A. Sjövall) and the Department of Psychiatry (Professor E. Essen-Möller) University of Lund, Sweden

THE COURSE AND OUTCOME OF THE POST PARTUM PERIOD FROM A GYNAECOLOGICAL AND GENERAL SOMATIC STANDPOINT

BY

L. JACOBSON, L. KAU AND A. NILSSON

We have previously reported on studies of psychiatric disorders in the post partum period. In these studies, based on randomly selected cases, special consideration was given to the incidence, symptomatology and various predisposing and prognostic factors (*Jacobson et al.* 1965 *Kau et al.* 1967 *Nilsson et al* 1967 a 1967 b) From these factors we now thought it of interest to analyse in more detail the gynaecological and general somatic factors. The post partum period is characterized by quantitatively important somatic adjustment processes, both retrogressive and progressive The present work aimed at elucidating normal and pathological variations of the course of these processes and the prognostic importance of various factors. Furthermore we wished to study to what extent the final results of these puerperal processes correspond to or deviate from the situation before the just completed pregnancy i.e. to investigate which permanent gynaecological and general somatic consequences will ensue from pregnancy and delivery Previous investigations into these problems seem to be few The return and nature of menstruation post partum was analysed in a large series by *Sharman* (1951) The changes in body weight during the first three months post partum have recently been studied by *Dennis* and *Bytheway* (1965) A general survey of the physiology and clinical course of the involution was presented by *Zilliacus* (1961) There appear to be

tion—were the anterior part of the uterine wall and the left lateral wall. In 17 per cent the rupture was incomplete.

Treatment was surgical in all cases except 5 where the patients died before operation was possible. In 56 (68 per cent) cases, total or subtotal hysterectomy was performed and in 22 (27 per cent) the uterus was repaired. Apart from cases in which laceration of the uterine musculature is extensive amputation has no advantage over suturation The frequency of complications was the same after both methods Repair is referable because it does not interfere with fertility

REFERENCES

Arfwedson H Nord. Med. *47* 895 1957
Badaway A. H The Lancet *2* 944 1960
Bak T F and *Hayden* G E. Amer J Obst & Gynec. *70* 961 1955
Beacham W D and *Beacham D W.*, Amer J Obst. & Gynec. *61* 824, 1951
Bjerre B Nord. Med *59* 601 1958
Bjerre B and *Astedt B* Acta obst. & gynec. scandinav *43* 1 1964
Boulle P and *Chrichton D* The Lancet *1* 360 1964
Eastman N J Obstetrics New York City Appleton-Century-Crofts Inc. p 942 1956
Englund S and *Odeblad E* Nord. Med. *44* 1992 1950
Ewing, H W Am J Obst. & Gynec. *74* 251 1957
Ferguson R. K. and *Reid D E* Am J Obst. & Gynec. *75* 172, 1958
Hedberg, G Nord. Med. *18* 1009 1943
Josey W E. Obst. Gynec. survey *18* 181 1963
Levi A. A. Obst. & Gynec. *18* 223 1961
Lundgren N and *Astedt B* Svenska Läkartidn. *60* 1037 1963
Pedowitz P and *Perell A.* Am J Obst. & Gynec. *76* 161 1958
Peretz A. and *Grünstein S* Gynecologia *1954* 287 1962
Pärnänen P O Acta obst. & gynec. scandinav *28* Suppl. *6* 1948
Turunen A. Gynecologia *147* 506 1959
Waters E G and *Hall W M* Obst. & Gynec. *20* 585 1962
Wachsman D V Am. J Obst. & Gynec. *66* 1197 1953
Weström L. Nord. Med. *63* 264 1960
Wilson A. L. Am. J Obst. & Gynec. *62* 1225 1951

Received on *May 21th, 1966*

Jacobson, L., Kaij, L., and Nilsson, Å. Acta obst. et gynec. scandinav. 46, 183, 1967
From the Department of Obstetrics and Gynaecology (Professor A. Sjövall)
and the Department of Psychiatry (Professor E. Essen-Möller) University of
Lund, Sweden

THE COURSE AND OUTCOME OF THE POST-PARTUM PERIOD FROM A GYNAECOLOGICAL AND GENERAL SOMATIC STANDPOINT

BY

L. JACOBSON, L. KAIJ AND Å. NILSSON

We have previously reported on studies of psychiatric disorders in the post partum period. In these studies, based on randomly selected cases, special consideration was given to the incidence symptomatology and various predisposing and prognostic factors (*Jacobson et al.*, 1965 *Kaij et al.* 1967 *Nilsson et al.* 1967 a 1967 b) From these factors we now thought it of interest to analyse in more detail the gynaecological and general somatic factors. The post-partum period is characterized by quantitatively important somatic adjustment processes, both retrogressive and progressive. The present work aimed at elucidating normal and pathological variations of the course of these processes and the prognostic importance of various factors. Furthermore we wished to study to what extent the final results of these puerperal processes correspond to or deviate from the situation before the just completed pregnancy *i.e.* to investigate which permanent gynaecological and general somatic consequences will ensue from pregnancy and delivery Previous investigations into these problems seem to be few The return and nature of menstruation post partum was analysed in a large series by *Sharman* (1951) The changes in body weight *during the first three months post partum* have recently been studied by *Dennis* and *Bytheway* (1965) A general survey of the physiology and clinical course of the involution was presented by *Zilliacus* (1961) There appear to be

tion—were the anterior part of the uterine wall and the left lateral wall In 17 per cent the rupture was incomplete.

Treatment was surgical in all cases except 5 where the patients died before operation was possible In 56 (68 per cent) cases, total or subtotal hysterectomy was performed and in 22 (27 per cent) the uterus was repaired. Apart from cases in which laceration of the uterine musculature is extensive amputation has no advantage over suturation The frequency of complications was the same after both methods Repair is referable because it does not interfere with fertility

REFERENCES

Arfwedson H Nord. Med. *47* 895 1952

Badawey A. H The Lancet *2* 944 1960

Bak T F and *Hayden G E* Amer J Obst. & Gynec. *70* 961 1955

Beacham W D and *Beacham D W.,* Amer J Obst. & Gynec. *61* 824 1951

Bjerre B. Nord. Med. *59* 601 1958

Bjerre B and *Astedt B* Acta obst. & gynec. scandinav *43* 1 1964

Boulle P and *Chrichton D* The Lancet *1* 360 1964

Eastman N J Obstetrics New York City Appleton-Century-Crofts Inc. p. 942 1956

Englund S and *Odeblad E* Nord. Med. *44* 1992, 1950

Ewing, H W Am. J Obst. & Gynec. *74* 251 1957

Ferguson R. K., and *Reid D E* Am. J Obst. & Gynec. *75* 172, 1958

Hedberg, G Nord. Med *18* 1009 1943

Josey W E. Obst. Gynec. survey *18* 181 1963

Levi A. A. Obst. & Gynec. *18* 223 1961

Lundgren N and *Astedt B.* Svenska Läkartidn. *60* 1037 1963

Pedowitz P and *Perell A.* Am. J Obst. & Gynec. *76* 161 1958

Peretz A. and *Grünstein S* Gynecologia *1954* 287 1962

Pärnänen P O Acta obst. & gynec. scandinav *28* Suppl. *6* 1948

Turunen A. Gynecologia *147* 506 1959

Waters E G and *Hall W M* Obst. & Gynec. *20* 585 1962

Wachsman D V Am. J Obst. & Gynec. *66* 1197 1953

Weström L. Nord. Med. *63* 264 1960

Wilson A. L. Am. J Obst. & Gynec. *62* 1225 1951

Received on May 21th, 1966

Jacobson, L., Kaij, L., and Nilsson, Å. Acta obst. et gynec. scandinav. 46, 183, 1967

From the Department of Obstetrics and Gynaecology (Professor A. Sjövall) and the Department of Psychiatry (Professor E. Essen-Möller) University of Lund Sweden

THE COURSE AND OUTCOME OF THE POST-PARTUM PERIOD FROM A GYNAECOLOGICAL AND GENERAL SOMATIC STANDPOINT

BY

L. JACOBSON, L. KAIJ AND Å. NILSSON

We have previously reported on studies of psychiatric disorders in the post-partum period. In these studies, based on randomly selected cases, special consideration was given to the incidence symptomatology and various predisposing and prognostic factors (*Jacobson et al.* 1965 *Kaij et al.* 1967 *Nilsson et al* 1967 a, 1967 b) From these factors we now thought it of interest to analyse in more detail the gynaecological and general somatic factors. The post partum period is characterized by quantitatively important somatic adjustment processes, both retrogressive and progressive The present work aimed at elucidating normal and pathological variations of the course of these processes and the prognostic importance of various factors. Furthermore, we wished to study to what extent the final results of these puerperal processes correspond to or deviate from the situation before the just completed pregnancy *i.e.* to investigate which permanent gynaecological and general somatic consequences will ensue from pregnancy and delivery Previous investigations into these problems seem to be few The return and nature of menstruation post partum was analysed in a large series by *Sharman* (1951) The changes in body weight during the first three months post partum have recently been studied by *Dennis* and *Bytheway* (1965) A general survey of the physiology and clinical course of the involution was presented by *Zilliacus* (1961) There appear to be

no detailed modern investigations on a broad scale in a representative sample concerning the somatic course and outcome of the post partum period

Material and Methods

The basic data for the investigation which is retrospective were collected from two sources the hospital records and an extensive questionnaire concerning somatic and mental symptoms and conditions The questionnaire was sent out on two occasions March and September 1964 to all women who had been delivered at the Department of Obstetrics and Gynaecology University of Lund during the first half of the months that lay 3 6 9 and 12 months prior to the questionnaire investigation (for details of the questionnaire and the methods of the investigation the reader is referred to our earlier articles) Thus the series was divided into various observation groups making it possible to study the different factors in relation to the post partum interval.

Only women who had given birth to a living child were included Patients with children which were stillborn or died in the neonatal period as well as those with twin pregnancies were excluded. The questionnaire was answered by 94 6 per cent of subjects The frequency of partially unanswered questions was very low The final series for the investigation consists of 861 women.

Results

Table I shows the distribution of the subjects with regard to age parity number of previous spontaneous abortions and interval from parturition *i.e* the time after delivery at which the questionnaire was sent out. Almost 3/4 of the subjects were below 30 years of age The frequency of women who had given birth to more than three children was less then 10 per cent. Thirteen per cent had a history of at least one spontaneous abortion a figure which is in close agreement with the overall incidence in the Department. Because practically all deliveries in Sweden take place in hospitals and obstetrical clinics the series is well representative of the population as a whole

Table I. Distribution of the Subjects with Regard to Age Parity and Time Interval from Parturition

Age (Years)	< 20		20–24		25–29		30–34	35–39		≥ 40
Number of patients	62		273		285		151	72		18
%	7.2		31 7		33 1		17.5	8.4		2.1
Parity	1	2	3	4	5	6	7	8	9	> 9
Number of patients	361	285	137	41	25	7	2	2	0	1
%	41.9	33.1	15.9	4.8	2.9	0 8	0.2	0.2	0	0 1
Previous spontaneous abortions				1	2 or more					
Number of patients				86	25					
%				10	3					
Observation groups—number of months from parturition				3	6	9	12			
Number of patients				239	226	212	184			
%				27.8	26.2	24.6	21 4			

Ninetytwo per cent of the subjects were married, 8 per cent unmarried or divorced 84 per cent lived in towns or densely populated areas 16 per cent in the countryside.

Of the children 457 (53 per cent) were boys, 404 (47 per cent) were girls. In 24 cases (2.8 per cent) the children were defined as premature *i.e* they had a birth-weight less than 2,500 g This frequency deviates from the total premature frequency of the Department (about 5 per cent) which is explained by the fact that the perinatal mortality is greatest among the premature infants, and that mothers with perinatally dead children were not included in our series. Surviving premature children belonged more often to primiparae (17 out of 361) than to multiparae (7 out of 500 $\chi^2 = 8.64$ 1 d.f $p < 0.01$)

Postnatal medical examination (normally within the first 2–3 months post partum) was made of 550 patients (64 per cent)

Table II summarizes the frequencies of the most *important* somatic complications during pregnancy delivery and the initial puerperal period, *i.e* when the patients were still in the Depart

Table II *Frequency of Different Obstetric Factors*

	Number	Per Cent
Pregnancy		
Toxaemia		
Slight	130	15.1
Moderate	34	3.9
Severe (pre-eclampsia)	13	1.5
Labour and delivery		
Prolonged labour (> 24 hours)	19	2.2
Operative vaginal delivery	47	5.5
Caesarean section	18	2.1
(Normal delivery	747	86.2)
Post-partum hemorrhage		
500–1000 ml	30	3.5
≥1000 ml	5	0.6
Puerperium (initial period of hospital stay after delivery)		
Uterine infection	29	3.4
Urinary tract infection	9	1.0
Infection of the breast	3	0.3
Thrombosis	1	0.1
Lying-in period after delivery		
< 6 days	486	56.4
6–9 days	327	38.0
> 9 days	48	5.6

ment. These figures are in good agreement with the total figures given in the annual statistical report of the Department. The initial puerperal factors should be compared with the results for the entire puerperal period, obtained by means of the questionnaire and reported below. The table shows that the frequencies of complications in the initial puerperal period were generally low.

Post partum Haemorrhage

It is well known through the studies of *Sheehan* and *Murdoch* (1938) that on rare occasions serious organic lesions in the hypo-

thalamic-hypophyseal system may develop as a consequence of large haemorrhages at the time of delivery In the present series no patients showed symptoms suggestive of such a lesion. The number of cases with large haemorrhages at delivery was low As Table II shows, 30 patients had haemorrhages of 500–1 000 ml, and 5 had haemorrhages exceeding 1 000 ml. The few cases naturally limit the statistical appraisal. However no correlation with genital involution return and nature of menstruation lactation or changes in body weight was found here. On the other hand, it should be mentioned that a statistically significant correlation existed between haemorrhage exceeding 500 ml at delivery and the occurrence of previous spontaneous abortions, patients with such large haemorrhages showing a higher frequency of abortions previously than did others ($\chi^2 = 6.10$ 1 d.f $p < 0.02$)

Changes in Body Weight

Changes in body weight were analysed from two basic points a) the differences between the weight of the subjects immediately before the recent pregnancy and at the time of the questionnaire b) the differences between the weight immediately post partum and at the time of the investigation The results are reported in Tables III and IV Table III shows that more than half of the subjects (54.5 per cent) weighed more at the time of the questionnaire than before the pregnancy and that in 16.0 per cent weight was unchanged in only 29.5 per cent was there a decrease of body weight. Taking the time which had elapsed between delivery and the investigation we found a significant difference between those groups delivered 3–6 months and those delivered 9–12 months before the investigation After 6 months, proportionately more subjects showed weight reduction than before this period at the same time the number of subjects whose weight had increased was relatively fewer ($\chi^2 = 22.84$ 4 d.f $p < 0.001$) Pregnancy and delivery in this series thus frequently resulted in a weight increase that persisted for a considerable period. It is noticeable that even one year after delivery 6.5 per cent of cases still showed a weight increase of more than 5 kg

In Table IV the body weight immediately post partum is com-

Table III. *Body Weight at the Time of Investigation Post Partum Compared with the Weight Before the Pregnancy*

	Reduced				Unchanged	Increased				No Information
	< 2 kg	2.1–5 kg	5 1–10 kg	> 10 kg		< 2 kg	2.1–5 kg	5 1–10 kg	> 10 kg	
umber	131	69	33	6	130	188	172	68	14	50
r cent	16 2	8.5	4 1	0 7	16 0	23.2	21.2	8 4	1 7	
	29 5 %					54.5 %				

Body Weight at the Time of Investigation Compared with the Weight Before the Pregnancy

Observation Groups (time after delivery)	Reduced		Un-changed	Increased		No Information
	≷ 5 kg	> 5 kg		≷ 5 kg	> 5 kg	
3–6 months	92	19	59	212	58	25
Per cent	20.9	4.3	13.4	48 2	13 2	
9–12 months	108	20	71	148	24	25
Per cent	29 1	5 4	19 1	39 9	6.5	

Table IV Body Weight at the Time of Investigation Compared with the Weight Imm diately P t P t m

	Reduced				Unchanged	Increased				N Information
	< 2 kg	2.1 5 kg	5.1 10 kg	> 10 kg		< 2 kg	2.1 5 kg	5.1 10 kg	> 10 kg	
Number	121	259	237	55	42	48	21	7	3	68
Per cent	15.3	32.6	29.9	6.9	5.3	6.1	2.6	0.9	0.4	
	84.7 %					10.0 %				

Body Weight at the Time of Investigation Compared with the Weight Imm di t ly Po t Pa t m

Observation Groups (time after delivery)	Reduced		Un-changed	Increased		No Informa-tion
	≷ 5 kg	> 5 kg		≷ 5 kg	> 5 kg	
3–6 month	227	126	25	37	6	44
Per cent	53.9	29.9	6.0	8.8	1.4	
9–12 months	153	166	17	32	4	24
Per cent	41.1	44.6	4.6	8.6	1.1	

pared with the weight at the time of the investigation. In general, 85 per cent of the subjects showed a weight decrease whereas 10 per cent showed an increase and 5 per cent no change during this period As in Table III we found also a statistically significant change of pattern at 6 months post partum. After this time, the number of subjects with weight decrease was proportionately higher and the frequency of those with weight increase somewhat lower ($\chi^2 = 19.43$ 4 d.f $p < 0.001$)

The correlations between weight changes post partum and psychiatric factors are reported by the authors in other papers (*Jacobson et al* 1965 *Kalj et al* 1967 *Nilsson et al* 1967 a)

The difference between body weight in the puerperal period and before pregnancy was also compared in cases with and without toxaemia during pregnancy Subjects who had some form of *toxaemia during pregnancy showed significantly poorer weight* regression than others ($\chi^2 = 55.5$ 4 d.f $p < 0.001$) However the total number of the toxaemic cases with weight increase being only 85 toxaemia cannot alone explain the weight changes in the whole series

Genital Involution

To assess involution, the following factors were studied duration of lochia (rubra and alba) the occurrence of occasional excessive haemorrhage or discharge during the first two months post partum and the time of resumption of menstruation These factors

Table V *Factors Reflecting the Genital Involution*

Lochia Rubra

	< 2 Weeks	2 W–4 W	> 4 W	Unanswered
No.	105	535	213	8
%	12.2	62.1	24.7	0.9

Lochia Alba

	< 1 Month	1–2 Months	> 2 Months	Unanswered
No.	423	357	65	16
%	49.1	41.5	7.5	1.9

	During the First Two Months Post Partum	
	Occasional Excessive Haemorrhage	Occasional Excessive Purulent Discharge
No.	236	192
%	27.4	22.3

Table VI. *Factors Significantly Correlated with Impaired Genital Involution (Percentage within Parentheses)*

		Impaired Involution	Normal Involution	χ^2	D.F	P
Age (years)	< 20	7 (3.9)	55 (8.1)			
	20–34	164 (91.1)	545 (80.0)	12.36	2	< 0.01
	≥ 35	9 (5.0)	81 (11.9)			
Parity	Primipara	92 (51.1)	269 (39.5)	7.85	1	< 0.01
	Multipara	88 (48.9)	412 (60.5)			
Return of menstruation	< 6 months post part.	128 (87.1)	551 (94.0)	7.90	1	< 0.01
	> 6 months post part.	19 (12.9)	35 (6.0)			
Amount of menstruation after return	Increased	47 (31.5)	135 (23.0)			
	Unchanged	79 (53.0)	397 (67.7)	11.92	2	< 0.01
	Decreased	23 (15.5)	54 (9.3)			
Feeling of flaccidity in abdominal and perineal musculature	Yes	48 (26.7)	123 (18.2)	6.33	1	< 0.02
	No	132 (73.3)	552 (81.8)			
Sexual adaptation	Coitus more painful	25 (15.1)	33 (5.3)			
	Unchanged	119 (71.7)	557 (89.1)	33.03	2	< 0.001
	Less painful	22 (13.2)	35 (5.6)			
Number of post partum mental symptoms	0–2	51 (28.3)	295 (43.3)			
	3–4	36 (20.0)	123 (18.1)	13.55	2	< 0.01
	≥ 5	93 (51.7)	263 (38.6)			

are summarized in Table V except for the resumption of menstruation which is accounted for in more detail below As Table V records about one-fourth of the subjects had lochia rubra for a period of more than four weeks as well as occasional excessive haemorrhage or discharge during the first two months.

In order to analyse prognostic and predisposing factors behind disturbances in genital involution the series was divided according to the occurrence of the following four symptoms a) lochia rubra for more than one month, b) lochia alba for more than two months c) occasional excessive haemorrhage and d) increased purulent discharge during the first two months post partum.

180 cases with 2–4 of the mentioned symptoms were classified as belonging to the group *impaired involution* others with one or none of the mentioned symptoms were classified as normal from the standpoint of involution It must be pointed out that in several cases with impaired involution the symptoms were not sufficient to necessitate a visit to a physician

The two groups showed no statistically significant difference regarding the following factors frequency of toxaemia during pregnancy and labour amount of post partum haemorrhage frequency of complications in labour and at delivery weight changes post partum duration of the lactating period, and frequency of nursing difficulties

Statistically significant differences however were found in the following respects (Table VI)

1 *Age* Subjects with impaired involution were found mostly in the age group 20–24 years whereas lower as well as higher age groups were under represented
2 *Parity* The frequency of primiparae was higher in the group with impaired involution than in the control group
3 *Duration of post partum amenorrhoea* Menstruation was found to return later in the group with impaired involution There was also a significant difference in the two groups of the proportion of subjects whose menstrual function returned to normal In those subjects with impaired involution both excessive and scanty menstrual periods were more common No

difference regarding the length of menstrual cycle could be demonstrated between the groups

4 *Muscular hypotonicity in the abdominal wall and the perineum.* Impaired genital involution was significantly correlated with subjective symptoms of impaired involution of the abdominal and perineal musculature. When judging this, the following must be noted In the total series, there were symptoms of imperfectly regained abdominal muscular tonicity in 171 cases (19.9 per cent) Gymnastic exercises post partum with the object of aiding the muscular involution in the abdominal wall and perineum and restoring tonicity are recommended and taught routinely to the patients at the Department. Such exercises, practised for a varying time after leaving the hospital were reported by 628 subjects (72.9 per cent) Significant negative correlation was found between the exercises and the frequency of impaired muscular tonicity Of those who had practised the exercises 16.3 per cent had an obvious feeling of muscular laxity whereas the corresponding frequency among subjects who had not practised the exercises was 30.2 per cent ($\chi^2 = 19.98$ 1 d.f $p < 0.01$) In the group with impaired genital involution 64.4 per cent of subjects reported that they had practised exercises of this kind as compared with 75.9 per cent in the group with normal genital involution. The difference is statistically significant ($\chi^2 = 9.22$ 1 d.f $p < 0.01$) It is thus possible that the correlation between impaired genital involution and impaired tonicity of the abdominal and perineal musculature is influenced by the practise of such exercises

It should also be mentioned here that a correlation, difficult to explain, was established between impaired muscular involution and a previous history of spontaneous abortions Subjects with a history of one or more abortions showed impaired involution of this kind significantly more often than did others ($\chi^2 = 4.17$ 1 d.f $p < 0.05$)

5 *Sexual adaptation.* No difference was found between the two groups regarding the time when sexual intercourse was recommenced post partum, nor regarding sexual satisfaction.

However the distribution of subjects with dyspareunia showed a significant difference. Impaired genital involution was associated more often with both increased and decreased incidence of dyspareunia as compared with the situation before pregnancy

6 *Psychiatric symptoms post partum.* Significant correlations were found between impaired genital involution and the number of mental symptoms in the puerperium. A detailed analysis concerning these facts is given in another study (*Nilsson et al*, 1967 a)

The Return and Nature of Menstruation

Table VII shows the variations concerning the time for the return of menstruation post partum This had occurred within 12 weeks in about half and within 24 weeks in over three-quarters of subjects These findings agree well with the report of for example, *Sharman* (1951) The return of menstruation must, of course be considered in relation to the lactation period Out of 116 subjects who had not begun to menstruate at the time of the investigation 96 (82 8 per cent) were *still breast feeding* As *Table VII* indicates the duration of lactation correlated with the time for the return of menstruation

Table VIII summarizes changes in the nature of menstruation as compared with before the pregnancy As shown in the table pregnancy and delivery often results in obvious changes in the type of *menstruation especially concerning amount and dysmenorrhoea* There was also found to be a relation between the time for the return and the nature of the menstrual cycle Thus, it seems that the earlier menstruation returns the shorter is the menstrual cycle and *vice versa* ($\chi^2 = 10\ 42$ 4 d.f $p < 0\ 05$) No correlation was found between time of return on one hand and amount and dysmenorrhoea on the other As reported above there is a relation between the course of genital involution and the time at which menstruation returns

Lactation

A total of 175 patients (20.3 per cent) reported that they had not breast fed 8 left the question unanswered. The length of the lactation period in those 678 cases (78.7 per cent) who had nursed to some extent is shown in Table IX. About 40 per cent of subjects ceased to breast feed within the first two months post partum, and almost 90 per cent during the first six months

Of the breast feeding subjects, 238 (35 1 per cent) reported that they had lactation difficulties of one or more kinds, whereas the other denied such complications with the exception of 35 subjects who left the question unanswered. Among lactation difficulties, shortage of milk dominated (163 cases) In 50 cases, some form of breast infection had occurred (lymphangitis or mastitis) and in 39 there had been difficulty in getting the children to suck.

The Resumption of Sexual Activity

At the time of the questionnaire investigation a total of 804 subjects (93 4 per cent) reported having resumed sexual intercourse Only 4 left the question unanswered. The time of resumption is given in Table X.

Concerning the sexual adaptation post partum, 58 women (7.3 per cent) reported increased pain at coition, and 57 (7.2 per cent) reduced pain, as compared with the situation prior to pregnancy In 159 cases (19.8 per cent) it was stated that sexual satisfaction had improved in comparison with the pre-pregnant state whereas in 92 cases (11.5 per cent) less satisfaction was described. In others, the sexual adaptation was reported as unchanged.

The time of return to coital activity was found to be related to the return of menstruation. Thus, 94.8 per cent of subjects whose menses had returned had resumed intercourse the frequency among the remainder of the series being 87.9 per cent. The difference is significant ($\chi^2 = 8.61$ 1 d.f $p < 0.01$) A similar relation existed to lactation Of those still breast feeding, 85 7 per cent had resumed intercourse as compared with 95.8 per cent of the remaining cases ($\chi^2 = 23.99$ 1 d.f $p < 0.001$) This is quite

However the distribution of subjects with dyspareunia showed a significant difference Impaired genital involution was associated more often with both increased and decreased incidence of dyspareunia as compared with the situation before pregnancy

6 *Psychiatric symptoms post partum* Significant correlations were found between impaired genital involution and the number of mental symptoms in the puerperium. A detailed analysis concerning these facts is given in another study (*Nilsson et al* 1967 a)

The Return and Nature of Menstruation

Table VII shows the variations concerning the time for the return of menstruation post partum This had occurred within 12 weeks in about half and within 24 weeks in over three-quarters of subjects These findings agree well with the report of for example, *Sharman* (1951) The return of menstruation must, of course be considered in relation to the lactation period. Out of 116 subjects who had not begun to menstruate at the time of the investigation, 96 (82.8 per cent) were still breast feeding As Table VII indicates the duration of lactation correlated with the time for the return of menstruation

Table VIII summarizes changes in the nature of menstruation as compared with before the pregnancy As shown in the table, pregnancy and delivery often results in obvious changes in the type of menstruation especially concerning amount and dysmenorrhoea There was also found to be a relation between the time for the return and the nature of the menstrual cycle. Thus, it seems that the earlier menstruation returns the shorter is the menstrual cycle and *vice versa* ($\chi^2 = 10\ 42$ 4 d.f $p < 0\ 05$) No correlation was found between time of return on one hand and amount and dysmenorrhoea on the other As reported above there is a relation between the course of genital involution and the time at which menstruation returns

Lactation

A total of 175 patients (20.3 per cent) reported that they had not breast fed 8 left the question unanswered. The length of the lactation period in those 678 cases (78 7 per cent) who had nursed to some extent is shown in Table IX. About 40 per cent of subjects ceased to breast feed within the first two months post partum, and almost 90 per cent during the first six months.

Of the breast feeding subjects, 238 (35 1 per cent) reported that they had lactation difficulties of one or more kinds whereas the other denied such complications with the exception of 35 subjects who left the question unanswered. Among lactation difficulties, shortage of milk dominated (163 cases) In 50 cases some form of breast infection had occurred (lymphangitis or mastitis) and in 39 there had been difficulty in getting the children to suck.

The Resumption of Sexual Activity

At the time of the questionnaire investigation, a total of 804 subjects (93 4 per cent) reported having resumed sexual intercourse. Only 4 left the question unanswered. The time of resumption is given in Table X

Concerning the sexual adaptation post partum, 58 women (7.3 per cent) reported increased pain at coition, and 57 (7.2 per cent) reduced pain, as compared with the situation prior to pregnancy In 159 cases (19.8 per cent) it was stated that sexual satisfaction had improved in comparison with the pre-pregnant state whereas in 92 cases (11.5 per cent) less satisfaction was described In others the sexual adaptation was reported as unchanged.

The time of return to coital activity was found to be related to the return of menstruation. Thus 94.8 per cent of subjects whose menses had returned had resumed intercourse the frequency among the remainder of the series being 87.9 per cent. The difference is significant ($\chi^2 = 8.61$ 1 d.f $p < 0.01$) A similar relation existed to lactation. Of those still breast feeding, 85 7 per cent had resumed intercourse as compared with 95.8 per cent of the remaining cases ($\chi^2 = 23.99$ 1 d.f $p < 0.001$) This is quite

However, the distribution of subjects with dyspareunia showed a significant difference. Impaired genital involution was associated more often with both increased and decreased incidence of dyspareunia as compared with the situation before pregnancy

6 *Psychiatric symptoms post partum* Significant correlations were found between impaired genital involution and the number of mental symptoms in the puerperium. A detailed analysis concerning these facts is given in another study (*Nilsson et al* 1967 a)

The Return and Nature of Menstruation

Table VII shows the variations concerning the time for the return of menstruation post partum This had occurred within 12 weeks in about half and within 24 weeks in over three-quarters of subjects These findings agree well with the report of for example *Sharman* (1951) The return of menstruation must, of course, be considered in relation to the lactation period. Out of 116 subjects who had not begun to menstruate at the time of the investigation, 96 (82 8 per cent) were still breast feeding As Table VII indicates the duration of lactation correlated with the time for the return of menstruation

Table VIII summarizes changes in the nature of menstruation, as compared with before the pregnancy As shown in the table, pregnancy and delivery often results in obvious changes in the type of menstruation especially concerning amount and dysmenorrhoea *There was also found to be a relation between* the time for the return and the nature of the menstrual cycle Thus it seems that the earlier menstruation returns the shorter is the menstrual cycle and *vice versa* ($\chi^2 = 10\ 42$ 4 d.f $p < 0\ 05$) No correlation was found between time of return on one hand and amount and dysmenorrhoea on the other As reported above there is a relation between the course of genital involution and the time at which menstruation returns

contrary to the observation of *Masters* and *Johnson* (1966) in their extensive study of the sexual response among American women With this exception however their findings concerning sexual response in the post partum period agree fairly well with ours

The relationship between sexual adaptation and response and the return of menstruation and the lactation period is found in Table XI Women in whom menstruation had returned reported improved satisfaction significantly more frequently than did the subjects who had not yet resumed menstruation. The situation was the same regarding those who were not breast feeding at the time of the investigation in comparison with the subjects who still were

A significant difference regarding the time of return to coital activity was found between those whose pregnancy had been planned and intentional and those whose pregnancy had not ($\chi^2 = 21.66$ 1 d.f $p < 0.001$) Concerning sexual adaptation and satisfaction however no significant differences occurred between these two groups.

As described above (Table VI) impaired genital involution had a significant influence upon the frequency of dyspareunia, but not on sexual satisfaction as compared with the pre-pregnant state

At the time of investigation, a total of 30 subjects reported that they were again pregnant. The distribution of these cases between the different post-partum time groups is shown in Table XII No further pregnancy was reported in the first observation group i.e 3 months post partum. All subjects with a further pregnancy had ceased lactation. In 28 of them, menstruation had returned, whereas in 2 cases, conception occurred during the amenorrhoeic period post partum.

Discussion

Because of its retrospective and purely statistical nature the investigation is mainly descriptive regarding the frequencies and intercorrelations of different gynaecological and other somatic variables during the post partum period. Naturally it permits few

Table VII *Time of the Return of Menstruation Post Partum*

	Not Returned at the Time of the Investigation	Returned After							
		⁊ 4 Weeks	5–8 Weeks	9–12 Weeks	13–16 Weeks	17–24 Weeks	25–26 Weeks	≥ 37 Weeks	Unanswered
	116	33	261	173	93	119	50	4	12
	13.5	3.8	30.3	20 1	10.8	13.8	5.8	0.5	1 4
mulated		3.8	34 1	54.2	65 0	78.8	84.6	85 1	

Relation between Time of Return of Menstruation and Lactation Period

Return of Menstruation	Breast Feeding		
	< 8 Weeks	8–24 Weeks	> 24 Weeks
⁊ 8 weeks	169 (66.5 %)	75 (29.5 %)	10 (4.0 %)
9–24 weeks	78 (22.8 %)	231 (67.5 %)	33 (9 7 %)
> 24 weeks	2 (4 %)	19 (37 %)	30 (59 %)

Table X. *Time of Resuming Sexual Intercourse Post Partum*

Time Post Partum	< 1 Month	1 3 Months	> 3 Months	No Answer or Unsure Regarding Time
Number of patients	5	704	83	12
Per cent of total number who reported resumed intercourse	0.6	87.6	10.3	1.5

conclusions about underlying physiological and patho-physiological mechanisms, but in our opinion it could serve as a guidance for clinical appraisals and management. The results show clearly that those processes which during the puerperium restore the body to its nonpregnant state vary within rather broad limits. It is also clear that the final result of the puerperal restitution processes does not, in many respects, imply a *restitutio ad integrum*. The completion of the pregnancy and delivery often produces permanent somatic changes, e.g. concerning the body weight, the nature of menstruation and the tonicity of the abdominal and perineal muscles as well as regarding the mental state, the latter being reported in more detail by the authors in others papers These changes are to some extent expressions of pathological disturbances, but must also be classified to a relatively high degree as physiological.

In this series, the body weight was generally greater in the puerperium than before pregnancy Although some reduction occurred within the first six months post partum, and a more pronounced reduction during the next six months, there was still a significantly higher average weight one year after delivery Pregnancy and delivery thus very often lead to an increase in body weight that remains for a considerable time In a recent investigation on a series of twins (*Cederlöf* and *Kaij* 1967) the weight increase in parous women, compared with nulliparae proved to be lifelong Subjects who had had some form of

Table VIII *The Nature of Menstruation at the Return Post Partum Compared with Before Pregnancy*

	Shorter Interval	Un changed	Longer Interval	Increased Amount	Un-changed	Decreased Amount	More Painful	Un-changed	Less Painful	Un-answered
Number	51	574	78	182	476	77	64	455	215	73
Per cent (of those who answered)	7.3	81.7	11.0	24.8	64.7	10.5	8.7	62.0	29.3	

Table IX. *Length of Lactation Period*

	Ceased Immediately after Return Home from Hospital	Lactation Period		
		< 8 Weeks	8–24 Weeks	24 Weeks
Number of patients	48	209	343	78
Per cent of the total number who breast fed	7.1	30.8	50.6	11.5

Table X. *Time of Resuming Sexual Intercourse Post Partum*

Time Post Partum	< 1 Month	1-3 Months	> 3 Months	No Answer or Unsure Regarding Time
Number of patients	5	704	83	12
Per cent of total number who reported resumed intercourse	0.6	87.6	10.3	1.5

conclusions about underlying physiological and patho-physiological mechanisms, but in our opinion it could serve as a guidance for clinical appraisals and management. The results show clearly that those processes which during the puerperium restore the body to its nonpregnant state vary within rather broad limits. It is also clear that the final result of the puerperal restitution processes does not, in many respects, imply a *restitutio ad integrum*. The completion of the pregnancy and delivery often produces permanent somatic changes, e.g. concerning the body weight, the nature of menstruation, and the tonicity of the abdominal and perineal muscles, as well as regarding the mental state, the latter being reported in more detail by the authors in others papers. These changes are to some extent expressions of pathological disturbances, but must also be classified to a relatively high degree as physiological.

In this series, the body weight was generally greater in the puerperium than before pregnancy. Although some reduction occurred within the first six months post partum, and a more pronounced reduction during the next six months, there was still a significantly higher average weight one year after delivery. Pregnancy and delivery, thus, very often lead to an increase in body weight that remains for a considerable time. In a recent investigation on a series of twins (Cederlöf and Kaij 1967), the weight increase in parous women, compared with nulliparae proved to be lifelong. Subjects who had had some form of

Table VIII *The Nature of Menstruation at the Return Post Partum Compared with Before Pregnancy*

	Shorter Interval	Un-changed	Longer Interval	Increased Amount	Un-changed	Decreased Amount	More Painful	Un changed	Less Painful	Un-answered
Number	51	574	78	182	476	77	64	455	215	73
Per cent (of those who answered)	7.3	81.7	11.0	24.8	64 7	10.5	8.7	62.0	29.3	

Table IX. *Length of Lactation Period*

	Ceased Immediately after Return Home from Hospital	Lactation Period		
		< 8 Weeks	8–24 Weeks	24 Weeks
Number of patients	48	209	343	78
Per cent of the total number who breast fed	7 1	30.8	50.6	11.5

toxaemia showed significantly greater weight increase than did others This is difficult to explain because the excess weight of the toxaemic patients immediately post partum is usually caused by oedema and the excess fluid is rapidly excreted (*cf Dennis* and *Bytheway* 1965) In many subjects the weight increase in the post-partum period is unquestionably caused by overeating, as evident, among other things, from correlations found between weight and mental factors (*Nilsson et al* 1967 a) However other factors for example endocrine no doubt also play a role. This assumption is supported by among others, experiences from long term administration of sex hormones for contraceptive pur poses

In about 29 per cent of cases the weight at the time of the investigation was lower than before pregnancy Usually this weight decrease was relatively small, but in isolated instances was as high as 10 kg or more. In these cases no correlation was found with the amount of post partum haemorrhage or with the course of genital involution factors which could argue for the occurrence of subclinical forms of hypopituitarism.

It is of interest to establish that symptoms of impaired genital involution did not show any statistical relations with duration of breast feeding or with the occurrence of lactation disturbances but were related to age and parity At the same time impaired involution seems to be a factor that predisposes to delayed return of menstruation.

The return of menstruation is in general primarily related to lactation As was observed also by *Sharman* (1951) the menstrual cycle will become shorter the earlier menstruation returns and *vice versa*. The duration of menstruation and the amount of menstrual flow showed in the main obvious changes as compared with the pre-pregnant state To what extent this should be inter preted as an expression of endocrine and other organic changes cannot be determined from this investigation.

The study strongly supports the value of gymnastic exercises during the puerperium with the intention of aiding the involution of the abdominal and perineal muscles and restoring the tonicity of these tissues

The return to coital activity and the sexual adaptation after

Table XI. *Relation Between Sexual Adaptation and Return of Menstruation Post Partum as Well as Lactation*

	Return of Menstruation	No return of Menstruation	χ^2	D.F	P
Coitus more painful	48	10			
Unchanged	590	6	5.97	2	N.S
Coitus less painful	44	13			
Decreased sexual satisfaction	66	24			
Unchanged	456	61	19 5	2	< 0.001
Improved sexual satisfaction	140	16			

	No Breast Feeding	Breast Feeding	χ^2	D.F	P
Coitus more painful	45	12			
Unchanged	547	124	0.26	2	N.S
Coitus less painful	44	11			
Decreased sexual satisfaction	59	32			
Unchanged	452	96	19.50	2	< 0 001
Improved sexual satisfaction	134	22			

Table XII. *Patients with a Further Pregnancy During the Period Between Delivery and Investigation*

Time of Investigation Post Partum	6 Months	9 Months	12 Months	Total
Number of patients	5	12	13	30
Per cent of total number within each observation group	_2	5.7	7 1	3.5

toxaemia showed significantly greater weight increase than did others This is difficult to explain because the excess weight of the toxaemic patients immediately post partum is usually caused by oedema and the excess fluid is rapidly excreted (*cf Dennis* and Bythesway 1965) In many subjects the weight increase in the post-partum period is unquestionably caused by overeating, as evident, among other things from correlations found between weight and mental factors (*Nilsson et al* 1967 a) However other factors for example endocrine, no doubt also play a role. This assumption is supported by among others, experiences from long-term administration of sex hormones for contraceptive pur poses

In about 29 per cent of cases the weight at the time of the investigation was lower than before pregnancy Usually this weight decrease was relatively small but in isolated instances was as high as 10 kg. or more. In these cases no correlation was found with the amount of post partum haemorrhage or with the course of genital involution factors which could argue for the occurrence of subclinical forms of hypopituitarism.

It is of interest to establish that symptoms of impaired genital involution did not show any statistical relations with duration of breast feeding or with the occurrence of lactation disturbances but were related to age and parity At the same time impaired involution seems to be a factor that predisposes to delayed return of menstruation.

The return of menstruation is in general primarily related to lactation. As was observed also by *Sharman* (1951) the menstrual cycle will become shorter the earlier menstruation returns and *vice versa*. The duration of menstruation and the amount of menstrual flow showed in the main obvious changes, as compared with the pre-pregnant state To what extent this should be interpreted as an expression of endocrine and other organic changes cannot be determined from this investigation.

The study strongly supports the value of gymnastic exercises during the puerperium with the intention of aiding the involution of the abdominal and perineal muscles, and restoring the tonicity of these tissues

The return to coital activity and the sexual adaptation after

Table XI *Relation Between Sexual Adaptation and Return of Menstruation Post Partum as Well as Lactation*

	Return of Menstruation	No return of Menstruation	χ^2	D.F	P
Coitus more painful	48	10			
Unchanged	590	76	5.97	2	N.S
Coitus less painful	44	13			
Decreased sexual satisfaction	66	24			
Unchanged	486	61	19.75	2	< 0.001
Improved sexual satisfaction	140	16			

	No Breast Feeding	Breast Feeding	χ^2	D.F	P
Coitus more painful	45	12			
Unchanged	547	124	0.26	2	N.S
Coitus less painful	44	11			
Decreased sexual satisfaction	59	32			
Unchanged	452	96	19.50	2	< 0.001
Improved sexual satisfaction	134	22			

Table XII. *Patients with a Further Pregnancy During the Period Between Delivery and Investigation*

Time of Investigation Post Partum	6 Months	9 Months	12 Months	Total
Number of patients	5	12	13	30
Per cent of total number within each observation group	2.2	5.7	7.1	3.5

ported and are usually low No serious somatic conditions were found.

The results from a detailed analysis are reported regarding the variations in body weight, return and nature of menstruation, lactation genital involution, involution of abdominal and perineal musculature return to coital activity and sexual adaptation. Frequencies and intercorrelations as well as changes, as compared with corresponding conditions before pregnancy are accounted for

REFERENCES

Cederlöf R., and Kaij L Acta Psych. Scand. 1967 (In print)

Dennis K. J and Bytheway W R. J J Obstet. Gynaec. Brit. Cwlth. 72 94 1963

Jacobson L. Kaij L. and Nilsson A. Brit. Med. J I· 1640 1965

Kaij L Jacobson L and Nilsson A. J Psychosom. Res. 10 317 1967

Masters W H and Johnson, V E., Human Sexual Response, Little Brown and Company Boston, Massachusetts 1966

Nilsson, A Kaij L. and Jacobson L J Psychosom. Res. 10 327 1967

Nilsson A. Kaij L and Jacobson L. J. Psychosom. Res. 10 341, 1967 b

Sherman A J Obstet. Gynaec. Brit. Emp 58 440 1951

Sheehan H L and Murdoch R. J Obstet. Gynaec. Brit. Emp 45 456 1938

Zilliacus, H Arch. Gynäk. 195 91 1961

Received on July 11th, 1966

completed pregnancy depend to a considerable extent on psychological factors In this investigation it is interesting to establish that the time for the resumption of sexual activity is obviously related to the time for the return of menstruation and the termination of lactation, as well as to planning of and wish for the pregnancy concerned Subjects with impaired genital involution reported greater variations than did others regarding improvement as well as worsening of dyspareunia and other discomforts during coitus as compared with before pregnancy No other factors with such predisposing effect were established.

Thirty women had conceived again at the time of the investigation. In two of them, conception occurred before menstruation had returned post partum

In conclusion this long term study of the post partum period shows that the puerperal processes and the return of bodily functions to the nonpregnant state can be very varied and that many women twelve months after delivery are still not completely restored regarding several gynaecological other somatic, and psychological factors. The investigation stresses the importance of directing particular clinical attention to this last-mentioned group of women Such subjects should also be subjected to further detailed studies from different scientific points of view

SUMMARY

In a representative sample of 861 women delivered of living children at the Department of Obstetrics and Gynaecology University of Lund the incidence and course of various gynaecological, sexual, and somatic factors during the post partum period were investigated and compared with the situation during the year prior to the completed pregnancy By dividing the sample into groups with different time intervals between delivery and investigation an analysis of the time relations of the factors during the first twelve months post partum was possible The study which is retrospective was based on information from the hospital records and on an extensive questionnaire.

The frequencies of clinical complications post partum are re-

sectio caesarea) oder die Untersuchungsmethoden sind zu unzulänglich um die gesamte Ausdehnung der Verwachsungen fest zustellen (z. B. Pneumoperitoneum) Objektive Routineuntersuchungen an klinischem Material fehlen.

Noch 1964 schreiben Backlund und Fries in ihrer Arbeit über die Ursachen des Adhäsionsileus und dessen Behandlung „Es ist gewöhnlich nicht möglich, den Effekt der Behandlung an einem klinischen Material zu kontrollieren. Und doch, es gibt bereits seit geraumer Zeit eine Möglichkeit, das Vorhandensein oder die Ausdehnung von postoperativen Verwachsungen korrekt zu studieren nämlich die direkte Beobachtung mit Hilfe der Laparoskopie. Diese sehr nützliche schon 1901 von Kelling und 1910 von Jacobaeus beschriebene Untersuchungsmethode ist bisher nicht in dem Ausmasse bei Untersuchungen dieser Art angewandt worden wie sie es verdient hätte. Noch im Jahre 1966 erscheint ein Kapitel über Adhäsionen in dem Buch „Acute and Chronic Iliac Pain in Women (Atlee 1966) in dem kein Wort über die Laparoskopie ja nicht einmal über die in Amerika sonst nicht ganz ungebräuchliche Culdoskopie gesagt wird. Für die Arbeit mit der weiblichen Sterilität und insbesondere natürlich mit den Problemen der Verwachsungen ist die Coelioskopie sei es auf dem transabdominalen (Laparoskopie) oder dem transvaginalen Wege (Culdoskopie) sozusagen eine *„conditio sine qua non* Verwachsungen sind ein wenn nicht sogar das Kernproblem der weiblichen Sterilität (nähere Einzelheiten siehe Swolin 1966 a, 1966 b)

Die Adhäsionsprophylaxe mittels Glukokortikoiden ist experimentell gut dokumentiert (Literatur bei Swolin 1966 a) Über eine intraperitoneale Anwendung von Glukokortikoiden zur Verhinderung von postoperativen Verwachsungen beim Menschen berichten Haße und Speth (1956) Zachariae und Zachariae (1956) Haße (1958) Virgili Marques (1960) Rust (1962) Japhet (1963) Borreman und Palmer (1964) Levy und Ducasse (1965) Bisher scheint die intraperitoneale Anwendung von Kortikosteroiden die besten Resultate zu geben. Im Vergleich mit den Tierversuchen sind die in der Klinik angewendeten Dosierungen doch recht niedrig. Deshalb wurde nach vorhergehenden Versuchen an Affen (Swolin, 1966 a)

Swolin K et Acta obst. et gynec. scandinav 46 204, 1967

Aus der Frauenklinik (Professor Sam Brody) der Universität in Göteborg, Schweden

DIE EINWIRKUNG VON GROSSEN INTRAPERITONEALEN DOSEN GLUKOKORTIKOID AUF DIE BILDUNG VON POSTOPERATIVEN ADHÄSIONEN

Klinische Studien mit Hilfe des Laparoskopes an operierten Extrauteringraviditäten

VON

KURT SWOLIN

„Saved by Surgery Killed by Adhesions so lautete der Titel eines Artikels des Redakteurs der Zeitschrift der Philippinischen Ärztegesellschaft (zit. Bridges *et al* 1965) Gewiss ist die Mortalität im Zusammenhang mit postoperativem Adhäsionsileus noch immer erschreckend hoch, – auch wenn man neueste Publikationen zu Rate zieht (Backlund und Fries 1964 8 % Weiss *et al* 1964 11 2 % Powley 1965 16 7 %) – Man braucht aber nicht nur die Todesfälle heranzuziehen um zu verstehen welche enorme Bedeutung und leider immer wieder neue Aktualität das Adhäsionsproblem vor allem für den chirurgisch tätigen Arzt hat

In der Literatur finden sich sehr viele Arbeiten die sich mit der Entstehung oder Verhütung von postoperativen Adhäsionen befassen (nähere Literaturhinweise Swolin 1966 a 1966 b) Meistens handelt es sich um Vorschläge oder tierexperimentelle Studien Wohldokumentierte klinische Studien sind selten Das Material dieser Untersuchungen kann wohl immer als eine gewisse Auslese betrachtet werden (z. B Reoperation infolge von Ileus Relaparotomie bei zweizeitigen Eingriffen oder wiederholter

In fast allen Fällen wurde ausser einer genauen Beschreibung dem Operationsbericht noch eine Skizze des Laparoskopiebefundes beigefügt. In einem einzigen Fall des hier angeführten Materials wurde die Nachkontrolle nicht wie gewöhnlich mit dem Laparoskop sondern bei einer erneuten Laparotomie 6 Wochen nach der ersten Operation durchgeführt.

In der Gruppe A wurden 71 Patientinnen operiert, von denen 37 Frauen nachuntersucht werden konnten. Die entsprechenden Zahlen für die Gruppe B sind 37 Operationen und 34 Nachuntersuchungen. Es war leider nicht möglich alle operierten Patientinnen nachzuuntersuchen. Mehrere Frauen waren an einen an deren Ort verzogen, andere waren nicht für eine Nachuntersuchung zu interessieren und einige waren nicht gemäss dem aufgestellten Behandlungsschema behandelt worden.

In der A-Gruppe wurden 8 Patientinnen erneut schwanger, 6 hatten eine normale Schwangerschaft und 2 einen Abort. In der B-Gruppe fanden sich 11 Patientinnen mit einer neuen Schwangerschaft. Hiervon verliefen 8 normal mit einem Partus, 1 war eine erneute Bauchhöhlenschwangerschaft und 2 endeten mit einem Abort (hierunter 1 abortus legalis).

Ergebnisse

Die Tabellen I und II geben eine kurzgefasste Zusammenstellung sowohl der nachuntersuchten Patientinnen der Gruppen A und B als auch der für diese Arbeit wichtigen Daten.

Bei der Zusammenstellung der Ergebnisse wurden die in der Tabelle III aufgeführten 5 Bezeichnungen zur leichteren Kennzeichnung der Verwachsungen eingeführt.

Fur die Gruppe A werden die Ausbreitung der Adhäsionen bei der Nachkontrolle, aufgeteilt in Fälle mit und ohne Hydrocortisongaben, das Ausmass der gelösten Verwachsungen bei der Operation der Bauchhöhlenschwangerschaft sowie etwaige neue Schwangerschaften mitgeteilt. NN bedeutet in der Tabelle, dass im Operationsbericht Adhäsionen nicht erwähnt wurden. Bei der Gruppe B wurde ausserdem noch der Versuch gemacht, die Blutmenge und das Ausmass von festsitzenden Coagula oder fibrinösen Auflagerungen zu beschreiben. Eine geschätzte Blut

beschlossen eine hoch dosierte Hydrocortisonprophylaxe der postoperativen Adhäsionen im klinischen Versuch zu studieren.

Material und Methode

Es wurde, um ein recht einheitliches Material zu erhalten, nur eine Gruppe von Operationen nämlich die in der Klinik operierten *Extrauteringraviditäten in die Untersuchung* einbezogen Von Anfang 1963 bis Anfang 1966 wurden die operierten Bauchhöhlenschwangerschaften fortlaufend in 2 Gruppen registriert. Gruppe A umfasste alle Operateure der Klinik abgesehen vom Verfasser dessen Operationen in der Gruppe B erfasst wurden.

Jede Patientin mit einer ungeraden Registrierungsnummer erhielt *vor Schluss der Bauchdecken eine intraperitoneale Instillation* von 2000 mg Hydrocortodrin® (Hydrocortisonacetat der Firma Astra Södertälje) Alle Patientinnen auch die ohne Kortikoidmedikation, bekamen während der Operation eine intravenöse Infusion von 0 7 g Syntodecin® auf 1000 ml Flüssigkeit (Rolitetra cyclinnitrat synthetisches Tetracyclinpräparat der Firma Astra Södertälje) In den ersten 7 Tagen post operationem erhielten alle *Patientinnen täglich viermal 1 Dragée Tetradecin Novum®* à 0,25 g (Tetracyclinhexametaphosphat der Firma Astra, Södertälje) Die Entfernung von Hautnähten geschah etwa am 7–8 Tag, die Entlassung etwa am 7–10 Tag

Es wurde versucht, die Patientinnen 3 Monate post operationem mit Hilfe von Hysterosalpingographie und Laparoskopie nachzuuntersuchen Die Untersuchung geschah etwa zum Ovula*tionstermin oder kurz vorher* Zuerst wurde eine Hysterosalpingographie mit Perjodal H viskös 35 % (wasserlösliches Röntgen kontrastmittel der Firma Pharmacia Uppsala) durchgeführt. Am nächsten Tag wurden die Patientinnen laparoskopiert. Die Durchgängigkeit der Eileiter wurde mit Hilfe von physiologischer mit Methylenblau gefärbter *Kochsalzlösung geprüft, das heisst* durch ein in die Cervix eingelegtes Instrument wurde die Farblösung via Uterus in oder durch die Eileiter gespült Mit Hilfe eines Photolaparoskopes wurde dann der jeweilige Befund dokumentarisch belegt (siehe z.B Abbildung 1–8)

In fast allen Fällen wurde ausser einer genauen Beschreibung dem Operationsbericht noch eine Skizze des Laparoskopiebefundes beigefügt. In einem einzigen Fall des hier angeführten Materials wurde die Nachkontrolle nicht wie gewöhnlich mit dem Laparoskop sondern bei einer erneuten Laparotomie 6 Wochen nach der ersten Operation durchgeführt.

In der Gruppe A wurden 71 Patientinnen operiert, von denen 37 Frauen nachuntersucht werden konnten. Die entsprechenden Zahlen für die Gruppe B sind 37 Operationen und 34 Nachuntersuchungen. Es war leider nicht möglich, alle operierten Patientinnen nachzuuntersuchen. Mehrere Frauen waren an einen anderen Ort verzogen, andere waren nicht für eine Nachuntersuchung zu interessieren und einige waren nicht gemäss dem aufgestellten Behandlungsschema behandelt worden.

In der A-Gruppe wurden 8 Patientinnen erneut schwanger: 6 hatten eine normale Schwangerschaft und 2 einen Abort. In der B-Gruppe fanden sich 11 Patientinnen mit einer neuen Schwangerschaft. Hiervon verliefen 8 normal mit einem Partus, 1 war eine erneute Bauchhöhlenschwangerschaft und 2 endeten mit einem Abort (hierunter 1 abortus legalis).

Ergebnisse

Die Tabellen I und II geben eine kurzgefasste Zusammenstellung sowohl der nachuntersuchten Patientinnen der Gruppen A und B als auch der für diese Arbeit wichtigen Daten.

Bei der Zusammenstellung der Ergebnisse wurden die in der Tabelle III aufgeführten 5 Bezeichnungen zur leichteren Kennzeichnung der Verwachsungen eingeführt.

Für die Gruppe A werden die Ausbreitung der Adhäsionen bei der Nachkontrolle aufgeteilt in Fälle mit und ohne Hydrocortisongaben, das Ausmass der gelösten Verwachsungen bei der Operation der Bauchhöhlenschwangerschaft sowie etwaige neue Schwangerschaften mitgeteilt. NN bedeutet in der Tabelle dass im Operationsbericht Adhäsionen nicht erwähnt wurden. Bei der Gruppe B wurde ausserdem noch der Versuch gemacht, die Blutmenge und das Ausmass von festsitzenden Coagula oder fibrinösen Auflagerungen zu beschreiben. Eine geschätzte Blut

Tabelle I. *Kontrollierte Patientinnen der Gruppe A*
(Bezeichnung der Verw. gemäss Tab. III)

Nr	Initialen	Verwachsungen bei Nachkontrolle		bei Op gefundene Verwachsungen	erneute Schwangerschaft
		mit Hydrocort.	ohne Hydrocort.		
2	H. M.		+	0	abortus
3	B. U.	0		0	
4	E. U.		+++	NN	
5	S. G.	0		0	
6	G. A.		++	++	
8	S. B.		++	0	
9	L. K.	0		++	
10	K. A.		+++	+++	
11	A. B.	0		0	partus
12	Ö. L.		++	++	partus
14	A. I.		+++	NN	
16	S. E.		+++	0	partus
17	E. U.	0		+++	
19	H. M.	0		+++	
20	H. A.		++	0	abortus
21	A. L.		++	0	
22	B. L.		+++	++	
23	B. G.	+		0	
24	P. U.		+++	NN	partus
25	S. E.		+++	++	
27	W. H.		+++	++	
31	A. B.	+		+	
32	Ö. K.		+++	+++	
33	K. L.	0		+++	
35	B. C.	(+)		+	
37	C. S.	++		+++	partus
38	N. G.		+++	0	
39	W. S.	0		0	
43	S. L.	++		++	partus
49	L. A.	0		+++	
50	L. M.		+++	+++	
52	H. K.		+	0	
54	S. M.		+++	NN	
55	I. E.	0		0	
57	L. I.	0		0	
63	B. M.	0		0	
66	K. B.		+++	0	

Tabelle II. *Kontrollierte Patientinnen der Gruppe B*
(Bezeichnung der Verw. gemäss Tab. III)

Nr.	Initialen	Verwachsungen bei der Nachkontrolle		bei der Operation gefundene			erneute Schwangerschaft
		mit Hydrocortison	ohne Hydrocortison	Verwachsungen	Blutmenge	Co- [illegible]	
1	H.L.	(+)		+	+++	+++	partus
2	L.S.		++	0	++	0	
4	E.B.		+++	0	++	(+)	abortus
5	K.S	0		++	+++	0	partus
6	H.S		+++	0	+	0	
7	A.M.	+		+	+	0	
8	R.S		+++	++	++	+	partus
9	E.A.	0		+++	0	+++	partus
10	W.B.		0	++	+	++	
11	L.K.	0		++	0	0	partus
12	F.E.		+++	+++	+++	0	
13	R.L.	+		++	0	0	X
14	A.L.		+++	+++	+	0	
15	O.B.	+		++	+	+++	partus
16	B.K.		++	++	+++	++	
17	F.K.	0		0	+++	0	
18	J.B		+++	0	+++	++	
19	H.K.	0		+++	++	+++	
20	G.S		+++	++	(+)	++	
21	A.R.	0		+	+++	0	partus
22	L.B.		+++	0	0	+++	
23	O.L.	+		++	++	+	
4	K.I		+++	+++	++	0	
25	M.G	0		+	+++	++	
26	O.E.		+++	+++	0	++	
27	H.I	0		+++	+	+++	abortus
28	K.J		+++	+++	++	0	
29	E.I	0		+++	+	0	
30	H.L.		0	0	+	+	
31	B.C	+		++	+	0	
32	G.B		+	0	+++	++	partus
33	A.L.	0		+	+++	+++	
34	J.B		+++	++	+	0	
36	F.U		+++	0	+++	+	

gefundene und gelöste Verwachsungen

Tabelle III. *Einteilung und Bezeichnung der Verwachsungen*

0	keine Verwachsungen
(+)	eine minimale Verwachsung
+	leichte Verwachsungen (einzelne dünne Stränge oder eine festere bis zu etwa 1 cm dicke Adhäsion)
++	mässige Verwachsungen (mehrere dünne, eventuell feste Stränge oder leichte Verwachsungen vom Typ + sowohl im kleinen Becken als auch unter der vorderen Bauchwand)
+++	reichliche Verwachsungen (ausgedehnte Adhäsionen an einer Stelle oder mässige Verwachsungen vom Typ ++ sowohl im kleinen Becken als auch unter der vorderen Bauchwand)
NN	Verwachsungen im Operationsbericht nicht erwähnt

(*siehe Abbildung 1–3*)

menge bis zu 50 ml wird in der Tabelle II mit + angegeben für 50–250 ml steht das Zeichen ++ und für eine Menge über 250 ml das Zeichen +++ Die Menge der Coagula wurde in der gleichen Tabelle mit + (gering) ++ (mässig) oder +++ (reichlich) gekennzeichnet.

Die Tabelle IV zeigt die Verteilung der Verwachsungen im gesamten Material, aufgeteilt in Gruppe A und B Diese beiden Gruppen sind dann wieder in Fälle mit und ohne intraperitoneale Hydrocortisonapplikation unterteilt.

Die statistische Bearbeitung der Ergebnisse bei der alle Fälle mit Verwachsungen – ob minimale oder reichliche – denen ohne Verwachsungen gegenübergestellt wurden ist mit Hilfe des χ^2-Testes durchgeführt worden um zu ermitteln ob eine Signifikanz im 5 % Niveau vorlag Es zeigte sich dass eine Hydrocortisonbehandlung eine signifikante Verminderung der Verwachsungen sowohl in der A Gruppe ($\chi^2 = 20{,}9$ ein Freiheitsgrad) wie auch in der B-Gruppe ($\chi^2 = 9{,}8$ ein Freiheitsgrad) bewirkt hatte

Die bei der Operation vorgefundenen Adhäsionen schienen nicht ohne Bedeutung für das Auftreten von Verwachsungen bei der Nachkontrolle zu sein (siehe Tab V a und V b)

Semm, Kurt, Acta obst. et gynec. scandinav. 46, 1967

Abbildung 1—8
Beispiele für postoperative Laparoskopiebefunde

Tabelle III. *Einteilung und Bezeichnung der Verwachsungen*

0	keine Verwachsungen
(+)	eine minimale Verwachsung
+	leichte Verwachsungen (einzelne, dünne Stränge oder eine festere bis zu etwa 1 cm dicke Adhäsion)
++	mässige Verwachsungen (mehrere dünne, eventuell feste Stränge oder leichte Verwachsungen vom Typ + sowohl im kleinen Becken als auch unter der vorderen Bauchwand)
+++	reichliche Verwachsungen (ausgedehnte Adhäsionen an einer Stelle oder mässige Verwachsungen vom Typ ++ sowohl im kleinen Becken als auch unter der vorderen Bauchwand)
NN	Verwachsungen im Operationsbericht nicht erwähnt

(siehe Abbildung 1–3)

menge bis zu 50 ml wird in der Tabelle II mit + angegeben für 50–250 ml steht das Zeichen ++ und für eine Menge über 250 ml das Zeichen +++ Die Menge der Coagula wurde in der gleichen Tabelle mit + (gering) ++ (mässig) oder +++ (reichlich) gekennzeichnet.

Die Tabelle IV zeigt die Verteilung der Verwachsungen im gesamten Material aufgeteilt in Gruppe A und B Diese beiden Gruppen sind dann wieder in Fälle mit und ohne intraperitoneale Hydrocortisonapplikation unterteilt.

Die statistische Bearbeitung der Ergebnisse bei der alle Fälle mit Verwachsungen – ob minimale oder reichliche – denen ohne Verwachsungen gegenübergestellt wurden ist mit Hilfe des χ^2 Testes durchgeführt worden um zu ermitteln ob eine Signifikanz im 5 %-Niveau vorlag Es zeigte sich, dass eine Hydrocortisonbehandlung eine signifikante Verminderung der Verwachsungen sowohl in der A-Gruppe ($\chi^2=20\,9$ ein Freiheitsgrad) wie auch in der B-Gruppe ($\chi^2=9\,8$ ein Freiheitsgrad) bewirkt hatte.

Die bei der Operation vorgefundenen Adhäsionen schienen nicht ohne Bedeutung für das Auftreten von Verwachsungen bei

Semm, Kurt Acta obst. et gynec. scandinav. 46 1967

Abbildung 1—8

Beispiele für postoperative Laparoskopiebefunde

Tabelle III. *Einteilung und Bezeichnung der Verwachsungen*

0	keine Verwachsungen
(+)	eine minimale Verwachsung
+	leichte Verwachsungen (einzelne, dünne Stränge oder eine festere bis zu etwa 1 cm dicke Adhäsion)
++	mässige Verwachsungen (mehrere dünne eventuell feste Stränge oder leichte Verwachsungen vom Typ + sowohl im kleinen Becken als auch unter der vorderen Bauchwand)
+++	reichliche Verwachsungen (ausgedehnte Adhäsionen an einer Stelle oder mässige Verwachsungen vom Typ ++ sowohl im kleinen Becken als auch unter der vorderen Bauchwand)
NN	Verwachsungen im Operationsbericht nicht erwähnt

(siehe Abbildung 1–3)

menge bis zu 50 ml wird in der Tabelle II mit + angegeben für 50–250 ml steht das Zeichen ++ und für eine Menge über 250 ml das Zeichen +++ Die Menge der Coagula wurde in der gleichen Tabelle mit + (gering) ++ (mässig) oder +++ (reichlich) gekennzeichnet.

Die Tabelle IV zeigt die Verteilung der Verwachsungen im gesamten Material aufgeteilt in Gruppe A und B Diese beiden Gruppen sind dann wieder in Falle mit und ohne intraperitoneale Hydrocortisonapplikation unterteilt.

Die statistische Bearbeitung der Ergebnisse bei der alle Fälle mit Verwachsungen – ob minimale oder reichliche – denen ohne Verwachsungen gegenübergestellt wurden ist mit Hilfe des χ^2 Testes durchgeführt worden um zu ermitteln ob eine Signifikanz im 5 % Niveau vorlag Es zeigte sich, dass eine Hydrocortisonbehandlung eine signifikante Verminderung der Verwachsungen sowohl in der A Gruppe ($\chi^2=20.9$ ein Freiheitsgrad) wie auch in der B-Gruppe ($\chi^2=9.8$ ein Freiheitsgrad) bewirkt hatte

Die bei der Operation vorgefundenen Adhäsionen schienen nicht ohne Bedeutung fur das Auftreten von Verwachsungen bei der Nachkontrolle zu sein (siehe Tab V a und V b)

Abbildung 1—8

Beispiele für postoperative Laparoskopiebefunde



Abb 1 Nahbild einer minimalen und einer leichten Verwachsung [Typ (+) und + gemäss Tab III] zwischen linker hinterer Tubenecke und dem Sigmoideum Im Hintergrund lig rotundum lig ovarii proprium, lig sacrouterinum und die mediale Hälfte eines mit etwas Bindegewebe bedeckten Ovarium.



Abb 2. Mässige Verwachsungen [Typ ++ gemäss Tab. III] zwischen deutlich aufgetriebener Saktosalpinx und linker Hinterwand des Uterus [Beachte welchen Nutzen man von der Anwendung des Metallstabes hat, eine Modifikation des von A. Sjövall (1963) empfohlenen Instrumentes, siehe ebenfalls Abb 3, 5, 7 und 8]



Abb 3 Reichliche Verwachsungen [Typ +++ gemäss Tab. III] an der Hinterwand des Uterus der Metallstab drückt den Uterus nach vorne und ermöglicht erst hierdurch eine Inspektion der reichlichen Verwachsungen.



Abb 4 Nahbild von maximal ausgespannten Netzteilen an der linken Seite der infraumbilikalen Verwachsungsplatte ausgedehnte Verwachsungen unter der vorderen Bauchwand zwischen omentum majus und der gesamten Operationsnarbe, im Hintergrund das Peritoneum de linken fossa iliaca



… 5. Nahbild eines grossen, normalen …mbrientrichters, der Metallstab ermöglicht …ne genaue Inspektion des Fimbrientrichters …, Lumen eines Teils der Tube erkennt man …ne beginnende Füllung mit Methylenblau-…sung. Keine Reaktion auf die am vorher…ehenden Tage durchgeführte Hystero-…alpingographie mit Perjodal H visköse 35 %



Abb. 6. Normales Übersichtsbild der Adnexe der rechten Seite. Keine Verwachsungen im kleinen Becken, im Hintergrund frei bewegliche Teile des Dünndarms. [Während der Operation der Tubargravidität wurde eine etwa 3 cm lange Resektion ohne *nachfolgende Naht der Tube selbst durchgeführt*, weiter erhielt die Patientin eine intraperitoneale Instillation von 2000 mg Hydrocortisonacetat am Schluss der Operation.]



Abb. 7. Gute Demonstration des Wertes einer Methylenblauinstillation während einer postoperativen Laparoskopie: die distale Hälfte der rechten Tube wird kräftig gewertet. Normales Hysterogramm und primär (ohne Methylenblau) normaler laparoskopischer Befund. 1 Monat später erneute Tubargravidität in derselben Tube.



Abb. 8. Deutlich sichtbare Methylenblaulösung in dem mit Hilfe des Metallstabes emporgehobenen Fimbrientrichter. Verwachsungen zwischen omentum majus und der medialen Kante des abdominalen Tubenendes. [Operation der Tubargravidität mit derselben Methodik wie bei der in Abb. 6 zitierten Patientin, doch keine Hydrocortisonacetatmedikation.]



Abb 1 Nahbild einer minimalen und einer leichten Verwachsung [Typ (+) und + gemäss Tab III] zwischen linker hinterer Tubenecke und dem Sigmoideum Im Hintergrund lig. rotundum, lig. ovarii proprium, lig sacrouterinum und die mediale Hälfte eines mit etwas Bindegewebe bedeckten Ovarium



Abb 2 Mässige Verwachsungen [Typ ++ gemäss Tab. III] zwischen deutlich aufgetriebener Saktosalpinx und linker Hinterwand des Uterus. [Beachte welchen Nutzen man von der Anwendung des Metallstabes hat, eine Modifikation des von A. Sjövall (1953) empfohlenen Instrumentes, siehe ebenfalls Abb 3 6, 7 und 8.]



Abb 3 Reichliche Verwachsungen [Typ +++ gemäss Tab III] an der Hinterwand des Uterus der Metallstab drückt den Uterus nach vorne und ermöglicht erst hierdurch eine Inspektion der reichlichen Verwachsungen.



Abb 4 Nahbild von maximal ausgespannten Netzteilen an der linken Seite der infraumbilikalen Verwachsungsplatte ausgedehnte Verwachsungen unter der vorderen Bauchwand zwischen omentum majus und der gesamten Operationsnarbe, im Hintergrund das Peritoneum der linken fossa iliaca



Abb. 5. Nahbild eines grossen, normalen Fimbrientrichters, der Metallstab ermöglicht eine genaue Inspektion des Fimbrientrichters. Im Lumen eines Teils der Tube erkennt man eine beginnende Füllung mit Methylenblaulösung, *keine Reaktion auf die am vorhergehenden Tage durchgeführte Hysterosalpingographie mit Perjodal H wäßr. 35 %.*



Abb. 6. Normales Übersichtsbild der Adnexe der rechten Seite, keine Verwachsungen im kleinen Becken, im Hintergrund frei bewegliche Teile des Dünndarms. [Während der Operation der Tubergravidität wurde eine etwa 3 cm lange Resektion ohne nachfolgende Naht der Tube selbst durchgeführt, weder erhielt die Patientin eine intraperitoneale Instillation von 2000 mg Hydrocortisonacetat am Schluss der Operation.]

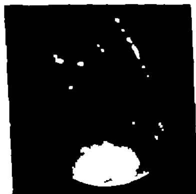


Abb. 7. Gute Demonstration des Wertes einer Methylenblauinstillation während einer postoperativen Laparoskopie: die distale Hälfte der rechten Tube wird kräftig gerötet, *normales Hysterogramm und primär (ohne* Methylenblau) normaler laparoskopischer Befund. 1 Monate später erneute Tubergravidität in derselben Tube.



Abb. 8. Deutlich sichtbare Methylenblaulösung in dem mit Hilfe des Metallstabes emporgehobenen Fimbrientrichter. Verwachsungen zwischen omentum majus und der medialen Kante des abdominalen Tubenendes. [Operation der Tubergravidität mit derselben Methodik wie bei der in Abb. 6 zitierten Patientin, doch keine Hydrocortisonacetatmedikation.]



Abb 1 Nahbild einer minimalen und einer leichten Verwachsung [Typ (+) und + gemäss Tab. III] zwischen linker hinterer Tubenecke und dem Sigmoideum. Im Hintergrund lig. rotundum, lg. ovarii proprium, lig. sacrouterinum und die mediale Hälfte eines mit etwas Bindegewebe bedeckten Ovarium.



Abb 2 Mässige Verwachsungen [Typ ++ gemäss Tab. III] zwischen deutlich aufgetriebener Saktosalpinx und linker Hinterwand des Uterus. [Beachte welchen Nutzen man von der Anwendung des Metallstabes hat, – eine Modifikation des von A. Sjövall (1953) empfohlenen Instrumentes, – siehe ebenfalls Abb. 3, 5, 7 und 8]



Abb 3. Reichliche Verwachsungen [Typ +++ gemäss Tab. III] an der Hinterwand des Uterus. der Metallstab drückt den Uterus nach vorne und ermöglicht erst hierdurch eine Inspektion der reichlichen Verwachsungen.



Abb 4 Nahbild von maximal ausgespannten Netzteilen an der linken Seite der infraumbilikalen Verwachsungsplatte ausgedehnte Verwachsungen unter der vorderen Bauchwand zwischen omentum majus und der gesamten Operationsnarbe, im Hintergrund das Peritoneum der linken fossa iliaca

Tabelle IV *Zusammenstellung der gesamten Verwachsungen aufgeteilt sowohl in Gruppe A und Gruppe B als auch weiter in Fälle mit und ohne intraperitoneale Hydrocortisonapplikation*
(Bezeichnung der Verw. gemäss Tab. III)

Gruppe A			
mit Hydrocortison		ohne Hydrocortison	
Typ der Verwachsungen	Anzahl der Patientinnen	Typ der Verwachsungen	Anzahl der Patientinnen
0	12	0	–
(+)	1	(+)	–
+	2	+	2
++	2	++	5
+++	–	+++	13
	17		20
Gruppe B			
0	10	0	2
(+)	1	(+)	
+	5	+	1
++	–	++	2
+++	–	+++	13
	16		18

Die Tendenz der Adhäsionsverminderung oder -verhinderung durch eine hochdosierte intraperitoneale Hydrocortisonapplikation zeigt sich ebenfalls in den Tabellen V a und V b.

Eine Zusammenstellung der Verwachsungen unter der vorderen Bauchwand findet sich in der Tabelle VI. Der Einfluss der Glukokortikoidtherapie auf die Neubildung von Verwachsungen ist hier besonders deutlich zu erkennen.

Anhaltspunkte für die Häufigkeit von postoperativen Adhäsionen in einem unausgelesenen Routinematerial ergeben sich bei der Betrachtung der Patientinnen ohne Hydrocortisonbehandlung in der Tabelle IV. In der A-Gruppe (20 Pat.) war keine Patientin ganz frei von Adhäsionen. In der B-Gruppe waren nur 2 von 18 Patientinnen ohne Verwachsungen. Fasst man beide Gruppen zusammen, so ergibt das eine Adhäsionsfreiheit in 2 von 38 Fällen,

Tabelle VI. *Zusammenstellung der Verwachsungen unter der vorderen Bauchwand, aufgeteilt sowohl in Gruppe A und Gruppe B als auch weiter in Fälle mit und ohne intraperitoneale Hydrocortisonapplikation* (*Bezeichnung der Verw. gemäss Tab. III*)

Gruppe A			
mit Hydrocortison		ohne Hydrocortison	
Typ der Verwachsungen	Anzahl der Patienten	Typ der Verwachsungen	Anzahl der Patienten
0	16	0	9
+		+	1
++	1	++	4
+++		+++	6
	17		20
Gruppe B			
0	16	0	8
+		+	1
++		++	2
+++		+++	7
	16		18

das sind 5,2 %. Gemäss der Tabelle IV dürften sich in etwa 68,4 % reichliche Adhäsionen finden.

Die hier angeführten klinischen Studien waren weder in der ersten Zeit post operationem noch bei der Nachkontrolle durch Komplikationen belastet.

Diskussion

Die Einteilung des gesamten Materials in eine Gruppe A und eine Gruppe B geschah aus folgendem Grund. Es sollten hierdurch zwei parallellaufende voneinander unabhängige Untersuchungsgruppen geschaffen werden, die später sozusagen als Kontrollmaterial füreinander dienen konnten. Ein Blick auf die verschiedenen Tabellen zeigt eine befriedigende Übereinstimmung der Ergebnisse beim Vergleich der Gruppe A mit der Gruppe B.

Durchgehende Versuche einer quantitativen Schätzung der

Tabelle V a. *Veränderungen des Ausmasses der Verwachsungen von der Operation bis zur laparoskopischen Nachkontrolle aufgeteilt sowohl in Gruppe A und Gruppe B als auch weiter in Fälle mit und ohne intraperitoneale Hydrocortisonapplikation*

Ausmass der Verwachsungen bei der Nachkontrolle	Gruppe A		Gruppe B	
	mit Hydrocort.	ohne Hydrocort.	mit Hydrocort.	ohne Hydrocort.
Abnahme	7	0	14	1
unverändert	9	5	2	6
Zunahme	1	11	0	11
	17	16	16	18

Tabelle V b. *Vergleich des Ausmasses der Verwachsungen bei der Operation mit dem Befund bei der laparoskopischen Nachkontrolle Zusammenfassung der gesamten Verwachsungen aufgeteilt in Fälle mit und ohne intraperitoneale Hydrocortisonapplikation (Bezeichnung der Verw gemäss Tab III)*

Patientinnen mit Hydrocortison

Verwachsungen bei der Operation	Verwachsungen bei der Nachkontrolle				
	+++	++	+	(+)	0
0	0	0	1	0	8
(+)	0	0	0	0	0
+	0	0	2	2	3
++	0	1	4	0	3
+++	0	1	0	0	8
	0	2	7	2	22

Patientinnen ohne Hydrocortison

Verwachsungen bei der Operation	Verwachsungen bei der Nachkontrolle				
	+++	++	+	(+)	0
0	8	4	3	0	1
(+)	0	0	0	0	0
+	0	0	0	0	0
++	7	3	0	0	1
+++	7	0	0	0	0
	22	7	3	0	2

Tabelle VI. *Zusammenstellung der Verwachsungen unter der vorderen Bauchwand aufgeteilt sowohl in Gruppe A und Gruppe B als auch weiter in Fälle mit und ohne intraperitoneale Hydrocortisonapplikation (Bezeichnung der Verw. gemäss Tab. III)*

Gruppe A			
mit Hydrocortison		ohne Hydrocortison	
Typ der Verwachsungen	Anzahl der Patienten	Typ der Verwachsungen	Anzahl der Patienten
0	16	0	9
+	-	+	1
++	1	++	4
+++		+++	6
	17		20
Gruppe B			
0	16	0	8
+		+	1
++		++	2
+++		+++	7
	16		18

das sind 5,2 %. Gemäss der Tabelle IV dürften sich in etwa 68,4 % reichliche Adhäsionen finden.

Die hier angeführten klinischen Studien waren weder in der ersten Zeit post operationem noch bei der Nachkontrolle durch Komplikationen belastet.

Diskussion

Die Einteilung des gesamten Materials in eine Gruppe A und eine Gruppe B geschah aus folgendem Grund. Es sollten hierdurch zwei parallellaufende, voneinander unabhängige Untersuchungsgruppen geschaffen werden die später sozusagen als Kontrollmaterial füreinander dienen konnten. Ein Blick auf die verschiedenen Tabellen zeigt eine befriedigende Übereinstimmung der Ergebnisse beim Vergleich der Gruppe A mit der Gruppe B

Durchgehende Versuche einer quantitativen Schätzung der

Tabelle V a. *Veränderungen des Ausmasses der Verwachsungen von der Operation bis zur laparoskopischen Nachkontrolle aufgeteilt sowohl in Gruppe A und Gruppe B als auch weiter in Fälle mit und ohne intraperitoneale Hydrocortisonapplikation*

Ausmass der Verwachsungen bei der Nachkontrolle	Gruppe A		Gruppe B	
	mit Hydrocort.	ohne Hydrocort.	mit Hydrocort.	ohne Hydrocort.
Abnahme	7	0	14	1
unverändert	9	5	2	6
Zunahme	1	11	0	11
	17	16	16	18

Tabelle V b *Vergleich des Ausmasses der Verwachsungen bei der Operation mit dem Befund bei der laparoskopischen Nachkontrolle Zusammenfassung der gesamten Verwachsungen aufgeteilt in Fälle mit und ohne intraperitoneale Hydrocortisonapplikation (Bezeichnung der Verw gemäss Tab III)*

Patientinnen mit Hydrocortison

Verwachsungen bei der Operation	Verwachsungen bei der Nachkontrolle				
	+++	++	+	(+)	0
0	0	0	1	0	8
(+)	0	0	0	0	0
+	0	0	2	2	3
++	0	1	4	0	3
+++	0	1	0	0	8
	0	2	7	2	22

Patientinnen ohne Hydrocortison

Verwachsungen bei der Operation	Verwachsungen bei der Nachkontrolle				
	+++	++	+	(+)	0
0	8	4	3	0	1
(+)	0	0	0	0	0
+	0	0	0	0	0
++	7	3	0	0	1
+++	7	0	0	0	0
	22	7	3	0	2

die Anzahl oder die Ausbreitung von Adhäsionen zu vermindern (Burger 1941 Seeley 1942 Levy und Ducasse 1965)

Nach den in dieser Arbeit vorgelegten Resultaten zu urteilen, besteht kein Zweifel an der Tatsache dass eine einmalige hochdosierte, intraperitoneale Hydrocortisonapplikation am Schluss der Operation imstande ist, das Ausmass von postoperativen Verwachsungen einzuschränken (siehe Tab IV–VI) Vorsichtshalber muss doch die Einschränkung gemacht werden dass diese Resultate nach der Operation von Bauchhöhlenschwangerschaften gefunden wurden, weshalb Schlüsse auf die Hydrocortisonwirkung bei nicht schwangeren Patientinnen mit dieser Reservation zu ziehen sind. Im Gange befindliche Untersuchungen des Verfassers deuten jedoch darauf hin dass eine Glukokortikoidtherapie auch bei nicht schwangeren Patientinnen den gewünschten Einfluss auf das Auftreten von postoperativen Verwachsungen ausübt.

Es zeigte sich, dass die intraperitoneale Instillation von sehr grossen Glukokortikoiddosen am Schluss der Operation anstandslos vertragen wurde und zu keiner Störung der Wundheilung führte (In dieser und anderen eigenen Untersuchungen haben bisher mehr als 100 Patientinnen 2000 mg Hydrocortison erhalten.)

70 postoperative Laparoskopien dieser Arbeit und mehr als 60 weitere postoperative Laparoskopien in anderen Studien des Verfassers bei ein bis dreimal im Unterbauch operierten Patientinnen verliefen komplikationslos. Hieraus ergibt sich, dass frühere Unterbauchoperationen, selbst wenn drei Operationsschnitte unterhalb des Nabels liegen, keine Kontraindikation für eine Laparoskopie sind.

Zusammenfassung

Laparoskopische Routinekontrollen von operierten Extrauteringraviditäten werden beschrieben. Jede zweite Patientin hatte eine intraperitoneale Hydrocortisonapplikation von 2000 mg erhalten. Die Gruppe der Patientinnen mit der sehr hoch dosierten Glukokortikoidtherapie zeigte eine statistisch signifikante Verminderung der postoperativen Adhäsionen. Die Instillation dieser sehr grossen Steroiddosen führte zu keinen Komplikationen Bei Patientinnen ohne Steroidtherapie fanden sich dagegen mehr oder weniger

Blutmenge und der festsitzenden Coagula sind in der Gruppe A nicht gemacht worden weshalb diese Angaben nur in die Tabelle II (Gruppe B) aufgenommen worden sind. Es fanden sich *keine sicheren* Anhaltspunkte für eine Relation zwischen Blutmenge oder (und) Coagula bei der Operation der Bauchhöhlenschwangerschaft und dem Vorhandensein oder der Ausdehnung *von postoperativen Verwachsungen bei der Kontrolle.*

Bei den mit Steroiden behandelten Patientinnen fanden sich 11 Schwangerschaften mit 9 Geburten die entsprechenden Zahlen *für die Patientinnen ohne Hydrocortison waren 8 bzw 5.* Das Material ist zu klein und die Beobachtungszeit zu kurz um hieraus bindende Schlüsse über einen eventuell günstigen Einfluss der Hydrocortisonbehandlung ziehen zu können

Riedels (1941) kurzgefasste Auffassung „Wo Verwachsungen sind, kommen auch wieder welche hin" darf wohl als der Ausdruck einer unter den chirurgisch tätigen Ärzten allgemein verbreiteten Ansicht aufgefasst werden Die in den Tabellen V a und V b angegebenen Zusammenfassungen über das Wiederauftreten von Verwachsungen bei Normalfällen – d.h. bei nicht mit Hydrocortison behandelten Patientinnen – geben eine objektive Bestätigung dieser Auffassung

Gemäss der Tabelle IV ist nach der Operation einer Bauchhöhlenschwangerschaft in etwa 95 % mit mehr oder weniger ausgebreiteten Verwachsungen in irgendeiner Form zu rechnen

Die in dieser Arbeit an Hand von routinemässigen Nachkontrollen gefundenen hohen Prozentzahlen betreffend das Auftreten von postoperativen Verwachsungen bei nicht mit Glukokortikoiden behandelten Patientinnen stimmen recht gut mit den von *anderen Verfassern* (Martin 1888 Kaufman 1935 Burger 1941 Green 1946 Benzer *et al* 1964) mit anderen Methoden gefundenen Zahlen überein nähere Einzelheiten finden *sich in der Arbeit von* Swolin (1966 b Tab I)

Betrachtet man die mit Hilfe des Pneumoperitoneum (z.B Naegeli 1919) gefundenen Werte findet man eine recht gute Übereinstimmung der Zahlen auch wenn man nur die Angaben über die Verwachsungen unter der vorderen Bauchwand (siehe Tab VI dieser Arbeit) zum Vergleich heranziehen will Es ist hierbei zu berücksichtigen dass eine Gravidität die Tendenz hat

was treated with hydrocortisone. Group A patients were operated by staff members with the exception of the author whose patients constituted group B. Photolaparoscopy was carried out 3 or more months after the operation

The results may be summarized as follows. One intraperitoneal application of 2000 mg of hydrocortisone acetate at the end of the operation prevents or diminishes the formation of post-operative intraperitoneal adhesions The results are statistically significant. The therapy with very large doses of hydrocortisone was not associated with any complications. Hitherto more than 100 patients (in this and other own studies) have received 2000 mg of hydrocortisone intraperitoneally

This study indicates that post-operative adhesions of varying extent will occur in 95 per cent of patients after pelvic surgery (in this study operation for ectopic pregnancy) if not treated with hydrocortisone. Furthermore, it is shown that there is a tendency in man toward recurrence of adhesions after previous operations where lysis of adhesions has been carried out

Previous operations even with one to three sub-umbilical incisions constitute no contraindication for laparoscopy This has been demonstrated on the 70 cases in this study and more than 60 additional cases in other studies by the author

LITERATURVERZEICHNIS

Allen H Acute and Chronic Iliac Pain in Women, Sec. Ed., Springfield, 966
Backlund E und *Fries, B* Nord. Med., 72, 878 964
Benzer H Blümel G und *Piza F* Klin. Med. (Wien) 19, 37 964
Borreman E. und *Palmer R.*, C. R. Soc. franç. Gynéc 34, 51 964
Bridges J Johnson, F und *Whiting, H* Acta anat. (Basel) 6 103, 965
Burger K Geburtsh. u. Frauenheilk., 3, 103, 1941
Green W J Indiana med Ass 39 634, 1946
Haße W und *Speth H* Beitr klin. Chir 193, 389, 956
Haße W Beitr klin. Chir 196 174 958
Jacobaeus H Münch. med. Wschr., 57 2090, 910
Jephet R., Bull. Féd. Soc. Gynéc. Obstét. franç 5 458 1963
Kaufmann E. Beitr klin. Chir 16 590, 1935
Kelling G 73 Vers. dtsch. Naturforscher und Ärzte Hamburg, 23. Sept. 901 zit. Münch. med. Wschr 57 2358 [illegible]
Levy E. und *Ducuing A.*, Ann. Chir. (Paris) [illegible]

ausgebreitete Verwachsungen in rund 95 % der Fälle. Weiter zeigte sich in dieser Patientinnengruppe die wohlbekannte Tendenz auf operativ gelöste Verwachsungen wieder mit Verwachsungen zu antworten Die komplikationslose Durchführung aller 70 Laparoskopien dieser Studie und von mehr als 60 weiteren postoperativen Laparoskopien in anderen eigenen Untersuchungen zeigt dass frühere Unterbauchoperationen – selbst wenn dreimal unterhalb des Nabels operiert wurde – keine Kontraindikation für eine Laparoskopie sind

Der Medizinischen Fakultät der Universität in Göteborg danke ich für die finanzielle Unterstützung dieser Arbeit. Für stete Hilfsbereitschaft bei der Planung und Durchführung der klinischen Studie und freundliche Zur verfügungstellung von Material und Mittel der Klinik bin ich meinem Chef Professor *Sam Brody* zu tiefem *Dank* verbunden. Dozent *Uno Zackrisson* von dem statistischen Institut der Universität in Göteborg bin ich für die *statistische Bearbeitung des Materials zu Dank verpflichtet.* Meinen Kollegen und dem Personal der Operationsabteilung der Frauenklinik I möchte ich meinen Dank aussprechen für die verständnisvolle Geduld und die liebenswürdige Hilfe bei den zeitraubenden Untersuchungen. Weiterhin möchte ich es nicht unterlassen an dieser Stelle meinen Dank zum Ausdruck zu bringen gegenüber meinen Lehrmeistern in der Laparoskopie Doktor Raoul Palmer Paris Oberarzt Hans Frangenheim Wuppertal, und Professor Alf Sjövall Lund.

SUMMARY

A clinical study in order to evaluate the effect of hydrocortisone on the prevention of post-operative intraperitoneal adhesions has been carried out on 108 patients for a three-year period. Routine follow up with photolaparoscopy has been performed on 70 subjects in order to record post-operative adhesions after surgery for ectopic pregnancy *Each second patient in the study* was treated with an intraperitoneal application of 2000 mg of hydrocortisone acetate at the end of the operation All the patients received an intravenous infusion of 0 7 g Syntodecin® (Rolitetra cycline nitrate) in 1000 ml of isotonic solution during operation Tetracycline therapy was continued orally for 7 days after the operation.

For the *purpose* of control the patients in the study had been divided into two groups in each of which every second patient

Swolin, Kurt, Acta obst. et gynec. scandinav. 46, 219, 1967

Aus der Frauenklinik (Professor Sune Brody) der Universität in Göteborg, Schweden

SPONTANHEILUNG NACH QUERRESEKTION DER TUBA FALLOPII

Beobachtungen an operierten Eileiterschwangerschaften

VON

KURT SWOLIN

In einer Studie am Affen wurde in einer früheren Arbeit (Swolin, 1966) gezeigt, dass die Tuba Fallopii nach einer Querresektion spontan heilen kann. Das heisst mit anderen Worten, in den zitierten Versuchen an Primaten kam es ohne eine Naht der Resektionskanten der Tube zu einer spontanen und komplikationsfreien Wiedervereinigung der resezierten Tubenteile. Aus wissenschaftlichen und rein praktischen Gründen war es wünschenswert zu wissen, ob auch die menschliche Tube in ähnlicher Weise zu reagieren vermag.

Die im folgenden angeführten Untersuchungen wurden an Eileitern mit einer Tubargravidität vorgenommen, da es aus naheliegenden Gründen praktisch unmöglich ist, derartige Studien an Frauen mit normalen Eileitern auszuführen. Für die Ergebnisse der hier angeführten Untersuchungen gilt also der Vorbehalt, dass sie an Eileitern mit einer Tubargravidität gewonnen wurden. – In welchem Sinne eine Tubargravidität die erzielten Ergebnisse beeinflussen könnte, mag einstweilen offen bleiben. Rein theoretisch könnte man sowohl negative als auch positive Beeinflussungen erwarten. –

Material und Methode

In den Jahren 1963–1966 wurde bei 14 Frauen die in der Klinik wegen einer Eileiterschwangerschaft operiert wurden nach einer

Martin A. Gynäkologenkongress 1888 zit. Vogel 1917
Naegeli Th., Zbl. Chir., 46 875 1919
Powley J Proc. Royal Soc. Med., 58 870 1965
Riedel zit. *Burger* 1941
Rust W Z. Geburtsh. Gynäk., *160* 79, 1962 1963
Seeley S., Amer J Surg., 56 579, 1942
Sjövall A., Acta obstet. gynec. scand., *42* 279 *1963*
Swolin K., Acta obstet. gynec. scand., *45* 451 1966 a
– Acta obstet. gynec. scand. *45* 473, 1966 b
Virgili-Marques A., Thèse de Paris 841 1960
Vogel K. Zbl. Chir., *44* 666 1917
Weiss A. *Adloff M.* und *Morand G* Strasbourg Méd. *15*, 165 1964
Zachariae F und *Zachariae L.* Ugeskr Laeg *118* 900 1956

Am 2. Aug. 1966 erhalten

Länge der Resektion	Aussehen der Resektionskanten bei der Op	Resektionshistologie der Tubenwand	Bemerkung
3–4 cm	sehr geschwollen und ödematös, recht grosse Differenz der Lumina	ödematöse und auf gelockerte Tubenwand	suspekte Salpingitis (nach abgelegtem m.III/ 965) vor der Nachuntersuchung
etwa cm	laterales Lumen bogenförmig mit Richtung nach unten zur Mesosalpinx und nicht zum Uterus	mässige Infiltration der Tubenwand mit Makrophagen und deciduaähnlichen Zellen	typische, kleine Endometrioseherde im Douglas (post op. unfreiwillig steril)
etwa 3 cm	ziemlich geschwollene und ödematöse Kanten	0 Detailinformation, graviditas tubaria	2000 mg Hydrocortisonacetat (p.n. 1966)
etwa 4 cm	medial, gut mm weites Lumen lateral, gut cm weites Lumen	deciduelle Stromareaktion im Parametrium, Tubenwand nicht engagiert	sehr grosse Lumendifferenz, 2000 mg Hydrocortisonacetat (p.n. 1966)
twa cm (mittleres Drittel)	ödematöse Kanten, lateraler Stumpf etwas livid, medial etwa 2 mm weites Lumen lateral, etwa 8 mm weites Lumen	Tubenwand mit kleinen Teilen normaler Schleimhaut und deutlicher deciduoeller Reaktion	bereits bei der Operation eine relativ kurze Tube (post op. freiwillig steril)
2,5 3 cm	ödematöse Kanten	ödematöse Tubenwand mit mässiger Entzündung	keine Resektion der Mesosalpinx, an medialer Resektionskante Blutstillung mit Thermokauter 2000 mg Hydrocortisonacetat (p.n. 966)
etwa 2,5 cm	stark S-förmiger Knick in der Endosalpinx der lateralen Resektionskante	gewellte, dünnwandige Tube	Endometriose im linken Ovarium und im rechten ligamentum sacrouterinum (p.n. 966)

Tabelle I. *Zusammenstellung der Befunde der 13 nachuntersuchten Patientinnen*

Laparoskopiebefund der resezierten Tube		Hysterosalpingographie der resezierten Tube		Jahr der Op	Resektionsstelle
Aussehen	Passage	Aussehen	Passage		
zusammengewachsen normale Konfiguration, an Beckenwand fixiert	nein	Füllung bis zum Anfang der Ampulle keine Auftreibung	nein	1963	zwischen mittlerem und lateralem Drittel
zusammengewachsen kurz	ja (?)	nur 2 cm, dann kleine Auftreibung	nein (schnelle Passage kontralat. Seite)	1964	1–2 cm lateral der Tubenecke
zusammengewachsen kurz, aber normale Konfiguration	nicht probiert, susp. intrauterine Gravidität	nur 2 cm, dann kleine Auftreibung	nein	1964	etwa 2 cm lateral der Tubenecke
nicht zusammengewachsen etwa 1 cm lange Diastase	durch medialen Stumpf der Diastase	Bild wie bei Laparoskopie	durch medialen Stumpf	1964	2–3 cm lateral der Tubenecke
zusammengewachsen kurz, etwas dicke Ampulle	ja	kurz, im übrigen keine Veränderungen	ja	1964	2–3 cm lateral der Tubenecke
zusammengewachsen etwas kurz, aber normale Konfiguration	ja	etwas grobe und gewundene Schleimhautfalten in der Ampulle	ja	1964	das mittlere Drittel
Verwachsungen verhindern Inspektion der lateralen 2/3 der Tube und des gesamten Ovarium		Kontrastfüllung bis zum Beginn der Ampulle	nein	1964	im mittleren Drittel

Länge der Resektion	Aussehen der Resektionskanten bei der Op	Routinehistologie der Tubenwand	Bemerkung
etwa 5 cm	recht normales Aussehen, sehr schmales Lumen medial	zellige Infiltration der Schleimhaut und der äusseren Schichten der Tube mit Leukocyten	Umstechung (Catgut 000 000) einer kleinen Arterie auf der medialen Resektionskante, 4 Umstechungen (Catgut 00 000) im Schlitz der Mesosalpinx (ab.incompl.m.III/ 966)
etwa 1,5 cm	kaum geschwollene Kanten, laterale Resektionskante recht livide	sehr geringe entzündliche, angedeutete deciduelle Reaktion	(derzeit grav. m. V)
etwa 3 cm		sehr dünne Wand mit Blutungen und sparsamer Leukocyteninfiltration	Laparoskopie zeigt durch Methylenblau gefüllte und geweitete Saktosalpinx auf der kontralat. Seite (post op. freiwillig steril)
etwa 3 cm		teilweise Infiltration mit einigen Chorionzellen und recht reichlicher Decidua	2000 mg Hydrocortisonacetat (post op. freiwillig steril)
etwa 3 cm		sparsame, teils nekrotische teils mit Leukocyten infiltrierte Decidua in der Tubenwand	2000 mg Hydrocortisonacetat (post op. freiwillig steril)
etwa 5-6 cm		stark geweitete ödematöse Tubenwand mit sparsamer Leukocyteninfiltration	2000 mg Hydrocortisonacetat (V-para, XII-gravida, post op. freiwillig steril)

Tabelle I (Forts.)

rt.	Laparoskopiebefund der resezierten Tube		Hysterosalpingographie der resezierten Tube		Jahr der Op.	Resektions-stelle
	Aussehen	Passage	Aussehen	Passage		
	zusammengewachsen etwas kurz, aber normale Konfiguration	ja	Ampulle etwas geweitet	Passage möglich, Bild nicht beweisend	1965	in der medialen Hälfte des mittleren Drittels
	zusammengewachsen, normale Konfiguration, Verwachsungen zwischen äusserster Ampulle und lateraler Beckenwand	ja	Kontrastfüllung bis zum medialen Teil der Ampulle	Passage möglich, Bild nicht beweisend	1965	zwischen mittlerem und laterale
0	scheinbar 2–3 cm lange Diastase mit dünner „Mesosalpinx zwischen Resektionskanten	nein	Ampulle kurz und etwas weit	ja Ampulle füllt sich schnell (vor kontralat. Seite)	1963	im mittlere Drittel
1	nur leicht zusammengewachsen, bei Blauinstillation platzt die Tube zwischen mittlerem und lateralem Drittel	nein	etwa 4 cm lange Füllung	nein	1965	im mittlere Drittel
2	zusammengewachsen; normale Konfiguration, vielleicht etwas schmaler an der Resektionsstelle	ja	angedeutete Erweiterung der Ampulle	ja	1965	zwischen mittlerem und laterale Drittel
3	kaum sichtbare Diastase kurz, normale Konfiguration	nein	etwa 1 5 cm lange Füllung	nein	1965	im mittleren Drittel

der Tabelle I ist der Versuch gemacht worden, die Befunde der 13 nachuntersuchten Patientinnen zusammenzufassen.

Mit Hilfe der Laparoskopie wurde gezeigt, dass der Eileiter in 9 Fällen wieder zusammengewachsen war. Bei einer weiteren Patientin bedeckten dichte Verwachsungen das gesamte Ovarium und die lateralen 2/3 der Tube, so dass eine Inspektion der Resektionsstelle unmöglich war. Bei Patientin Nr. 10 zeigte sich im Laparoskop das Bild einer scheinbaren etwa 2–3 cm langen Diastase. Man hatte den Eindruck eines sehr kurzen medialen Resektionsstumpfes und eines mehr als die Hälfte der Tubenlänge ausmachenden lateralen Resektionsstumpfes, die in einem sanften Übergang durch ein schmales Band verbunden waren, welches als Mesosalpinx aufgefasst wurde. Dieses „schmale Band" erstreckte sich etwa über die laterale Hälfte des medialen Drittels und die mediale Hälfte des mittleren Drittels einer im übrigen normal dicken und im Vergleich mit der kontralateralen Seite normalkonfigurierten Tube. Die Methylenblauinstillation zeigte keine Passage weder auf der resezierten noch auf der kontralateralen Seite. In zwei Fällen fand sich eine echte Diastase der Resektionskanten die eine etwa 1 cm, die andere etwa 1 mm lang.

In 5 Fällen (Pat. Nr. 5, 6, 8, 9 und 12) sah man eine einwandfreie Passage der in die Cervix instillierten Methylenblaulösung durch den Fimbrientrichter der resezierten Tube (siehe z.B. Abb. 8 Swolin, K. Acta obstet. gynec. scand., 46, 204, 1967). In einem weiteren Fall (Pat. Nr. 2) sollte man, um ganz korrekt zu sein, eine augenscheinliche Passage der Blaulösung mit einem kleinen Fragezeichen versehen. – Aufgrund von zahlreichen Verwachsungen machte die Inspektion der Fimbrien bedeutende Schwierigkeiten. Dadurch lag eine gewisse Zeitspanne zwischen der Inspektion der kontralateralen und der resezierten Seite, weshalb die Möglichkeit einer Kontamination der Fimbrien durch die Farblösung der kontralateralen Seite nicht mit Sicherheit auszuschliessen war, wenn auch diese Möglichkeit als sehr unwahrscheinlich betrachtet werden musste. –

In drei Fällen (Pat. Nr. 5, 6 und 12) liess sich der laparoskopische Befund der Passage auch durch das Röntgenbild einwandfrei belegen (siehe Abb. 1–3). Bei einer weiteren Patientin (Nr. 10) zeigte das Röntgenbild eine einwandfreie Füllung und schnelle

mehr oder weniger ausgedehnten (siehe Tab I) Querresektion eines Teils der graviden Tube keine Vereinigung der Resektions kanten der Tube selbst durchgeführt. Es wurde nur eine exakte Blutstillung mit dem Thermokauter oder mit feinen Umstechungen und eine Naht oder eine Adaptation des Mesosalpinxschlitzes durchgeführt. 10 Patientinnen wurden vom Verfasser selbst operiert die übrigen 4 Frauen hatten 3 andere Ärzte der Klinik als Operateure

Alle 14 Patientinnen erhielten gemäss der in einer vorhergehenden Arbeit beschriebenen Methodik (Swolin, 1967) während der Operation eine intravenöse Infusion von 0 7 g Syntodecin® auf 1000 ml Flüssigkeit (Rolitetracyclinnitrat synthetisches Tetracyclinpräparat der Firma Astra Södertälje) Weiter bekamen sie in der ersten postoperativen Woche per os viermal täglich ein Dragée Tetradecin Novum® à 0 25 g (Tetracyclinhexametaphosphat der Firma Astra Södertälje)

Am Schluss der Operation hatten 6 der 14 Patientinnen eine intraperitoneale Instillation von 2000 mg Hydrocortodrin® erhalten (Hydrocortisonacetat der Firma Astra, Södertälje)

Die Nachuntersuchungen geschahen frühestens drei Monate nach der Operation und wurden mit Hilfe von Hysterosalpingographie und Photolaparoskopie kurz vor oder etwa während der Ovulationszeit durchgeführt Als Kontrastmittel wurde das Per Jodal H viskös 35 % verwendet (wasserlösliches Röntgen kontrastmittel der Firma Pharmacia Uppsala) Die Laparoskopie wurde fast immer am Tage nach der Hysterosalpingographie aus geführt. Die Durchgängigkeit der Eileiter wurde hierbei mit physiologischer Kochsalzlösung die mit Methylenblaulösung gefärbt war geprüft Die Instillation geschah durch eine in die Cervix eingeführte Gynographkanüle (Weisman, 1951) Bei einer Patientin wurde wegen des Verdachtes einer eventuel len *intrauterinen Gravidität* keine *Blauinstillation* während der Laparoskopie durchgeführt. Aus demselben Grunde wurde die Hysterosalpingographie erst später durchgeführt.

Ergebnisse

Von den 14 Patientinnen konnten 13 nachuntersucht werden eine der vom Verfasser operierten Patientinnen ist verzogen In



Abb Passage durch die resezierte und nicht genähte linke Tube (Pat. N 5).



Abb Passage durch die resezierte und nicht genähte rechte Tube (Pat. Nr 6)

Passage der resezierten Tube (siehe Abb. 4) ohne dass es möglich war dies bei der am folgenden Tage durchgeführten Laparoskopie zu bestätigen In zwei anderen Fällen (Pat. Nr 8 und 9) sagte der Röntgenologe bei der genauen Kontrolle der Hysterosalpingogramme dass die Passage möglich aber nicht mit Sicherheit zu beweisen war

7 der 13 Patientinnen hatten bisher eine intrauterine Graviditat post op (4 part norm., 1 ab incompl m. III 1 ab leg m. III 1 Pat ist derzeit schwanger 5 Pat sind freiwillig steril und nur eine einzige ist unfreiwillig steril)

Operationen und Nachkontrollen waren durch keine Komplikationen belastet.

Diskussion

Eine Spontanheilung von querresezierten Tuben mit nicht bei der Operation vereinigten Tubenstümpfen ist nicht nur im Tierversuch an Affen sondern auch beim Menschen möglich. Durch die im vorstehenden angeführten Untersuchungen ist bewiesen worden dass ein spontanes Zusammenwachsen von während der Operation nicht vereinigten Tubenteilen nach der Resektion eines Teils des Eileiters aufgrund einer Tubargravidität eintreten kann (siehe Abb 6 Swolin K Acta obstet. gynec scand. 46 204 1967) Dies rein makroskopische auf die Anatomie bezogene Beobachtung konnte in 9 von 12 Fällen gemacht werden (Patientin Nr 7 scheidet hierbei aus da Verwachsungen eine Inspektion der Resektionsstelle verhinderten) Die Patientin Nr 10 mit der röntgenologisch einwandfreien Passage und der schmalen Verbindung im laparoskopischen Bild darf wohl auch zu der Zahl der zusammengewachsenen Tuben gerechnet werden. Somit wären es also 10 von 12 kontrollierbaren Fällen Allerdings platzte dann bei der Methylenblauinstillation die Anastomose bei einer Patientin (Pat. Nr 11)

Eine laparoskopische oder röntgenologische Passage durch die resezierte Tube konnte bei 6 (evtl 7 falls man Fall Nr 2 mitrechnet) von 13 nachuntersuchten Patientinnen nachgewiesen werden. Bei 3 Patientinnen fand sich eine einwandfreie Durchgängigkeit sowohl im laparoskopischen als auch im röntgenologischen Befund Bei der Besprechung der Resultate im Hinblick



Abb. 5 Ausbuchtung in der lateralen Hälfte des mittleren Drittels der rechten Tube knapp 4 Monate vorher expressio et excochleatio ovi. Die Auftreibung liess sich auch durch Methylenblauinstillation während der Laparoskopie verifizieren. (Beacht die sicherlich pathologische Kontrastansammlung im entsprechenden Teil der makroskopisch völlig normalen linken Tube.)



Abb. 6 Normales Röntgenbild 5 Monate nach sectio tubae dx ebenfalls im Laparoskop normale Konfiguration. Erst die Methylenblauinstillation während der Laparoskopie ergibt ein pathologisches Bild (siehe Abb. 7 Swoln K 46 204 967)



Abb. 3 Passage durch die resezierte und nicht genähte rechte Tube (Pat. Nr 12) Das Kontrastmittel rinnt schneller durch die operierte Seite und hat sich bereits verteilt.



Abb. 4. Passage durch die resezierte und nicht genähte rechte Tube (Pat. Nr 10) Das Kontrastmittel rinnt durch die operierte Seite noch bevor die Füllung der kontralateralen Seite begonnen hat.



Abb. 5 Ausbuchtung in der lateralen Hälfte des mittleren Drittels der rechten Tube knapp 4 Monate vorher expressio et exochleatio ovi. Die Auftreibung ließ sich auch durch Methylenblauinstillation während der Laparoskopie verifizieren. (Beacht die sicherlich pathologische Kontrastansammlung im entsprechenden Teil der makroskopisch völlig normalen linken Tube.)



Abb. 6. Normales Röntgenbild 5 Monate nach sectio tubae dx., ebenfalls im Laparoskop normale Konfiguration. Erst die Methylenblauinstillation während der Laparoskopie ergibt ein pathologisches Bild (siehe Abb 7 Swolin K., 46 204 1967)



Abb. 7 Trotz sorgfältiger Naht der Anastomose nach resectio tubae ein Diastase in der lateralen Hälfte des mittleren Drittels. Etwas Kontrastmittel rinnt durch die laparoskopisch verifizierte Diastase.

auf eine Durchgängigkeit ist weiterhin anzumerken dass eine Patientin (Nr 1) vor der Nachuntersuchung eine auspekte Salpingitis hatte (erhielt deshalb Antibiotica) die durchaus einen ungünstigen Einfluss auf den Befund bei der späteren Nachuntersuchung ausgeübt haben kann.

Eine Diskrepanz zwischen laparoskopischem und röntgenologischem Befund fand sich in 3 (evtl. 4) Fällen. Gibt es eine Möglichkeit, eine solche Diskrepanz zu erklären? Für den Röntgenologen, der sich viel mit gynäkologischer Diagnostik befasst, ist es keine unbekannte Tatsache dass sich eine Tube mitunter schneller füllt und leert – wenn überhaupt – oder sich auch gar nicht füllt, trotz eines bilateral völlig normalen Bildes bei einer anderen zeitlich nicht weit entfernten Untersuchung (Stattin, 1966) Vielleicht bewirkt ein schneller Abfluss der einen Seite eine mangelnde Füllung oder Passage der kontralateralen Seite Ein partieller Spasmus oder eine Schleimhautschwellung könnte auch für eine Seitendifferenz verantwortlich gemacht werden. Weiter begrenzt die Möglichkeit eines Kontrastüberfliessens auf die kontralaterale Seite die Beweiskraft des Röntgenbildes Auf alle Fälle ist zu beachten, dass in den 2 Fällen mit der röntgenologisch nicht ganz einwandfreien Passage über das Ostium hinaus das Kontrastmittel in dem einen Fall (Nr 8) sicher und in dem anderen Fall (Nr 9) wahrscheinlich über die Resektionsstelle hinausging. Für den an der Laparoskopie interessierten Gynäkologen ist es weiterhin keine Neuigkeit, dass Laparoskopie und Röntgenbild voneinander abweichen können (Swolin und Rosencrantz) Die Narkose der Patientin und der bessere Überblick über die Aussenseite der Tube schaffen mitunter für die Laparoskopie Voraussetzungen, zu einem vom Röntgenbild etwas abweichenden und bisweilen auch umfassenderen Befund zu kommen. Es kann aber auch der umgekehrte Fall eintreten, wie sich leicht am Beispiel der Patientin Nr 10 anschaulich machen lässt. – Vielleicht mag in diesem Falle eine mangelnde Abdichtung mit einem Reflux der Blaulösung aus der Cervix (Saugglocke während der Hysterosalpingographie Weismaninstrumentarium während der Laparoskopie) eine gewisse Rolle gespielt haben vielleicht kann eine leichte Reizung der Schleimhaut des schmalen intramuralen oder isthmischen Tuben-

teils nach der Röntgenuntersuchung des vorhergehenden Tages die Durchgängigkeit erschwert haben. In keinem der hier beschriebenen Fälle wurde jedoch im Laparoskop eine entzündliche Reaktion der Fimbrien auf die vorausgegangene Hysterosalpingographie beobachtet. –

Eine Diskrepanz zwischen röntgenologischem und laparoskopischem Befund erlaubt vielleicht auch mitunter gewisse Schlüsse auf den funktionellen Zustand der Tube ziehen zu können. Auf keinen Fall ist es jedoch berechtigt hieraus zu folgern, dass die eine Methode der anderen überlegen sei Beide haben ihre teilweise voneinander abweichenden Indikationen, Vorzüge und Grenzen.

Betrachtet man die verschiedenen Fakta der Tabelle I so findet man keinen bindenden Beweis für einen bedeutenden Einfluss der Resektionsstelle auf eine gute Restitution. Es ergibt sich jedoch der Eindruck, dass es vielleicht günstiger ist, eine Resektionsstelle im mittleren Drittel zu haben Eine Schwellung oder ödematöse Auftreibung der Resektionskanten sowie eine instrumentelle Blutstillung an diesen während der Operation scheinen nicht die Prognose für eine gute Restitution zu verschlechtern Eine zu grosse Differenz der Lumenweite der Resektionskanten (Fall Nr 4) und ein nicht gerader auf die gegenüberliegende Resektionskante gerichteter Verlauf der Endosalpinx (Fall Nr 2 und 7) sind vielleicht ebenso wie eine zu grosse Resektionslänge (Fall Nr 4 und 13) ungünstig für gute Resultate Ein Einfluss der intraperitonealen Hydrocortisonapplikation auf die Durchgängigkeit der resezierten und zusammengewachsenen Tuben lässt sich nicht feststellen. Die beiden Fälle mit der makroskopischen Diastase finden sich jedoch in der Gruppe der mit Glukokortikoid behandelten Frauen Die Betrachtung der Befunde der mikroskopisch untersuchten Präparate erlaubt keinen bindenden Schluss in einer bestimmten Richtung

Fragt man sich welchen praktischen Nutzen man aus den im vorstehenden zitierten Untersuchungen und Resultaten ziehen kann so ergeben sich für den operierenden Gynäkologen zwei Situationen für eine mögliche Anwendung in der Praxis. Dies ist bei der Operation von Eileiterschwangerschaften und bei Tubarplastiken. Die Sterilitätsoperationen – eigentlich sollte man

Fertilitätsoperationen sagen – gehören nach Martius (1960) zu den häufigen Eingriffen in der Gynäkologie. Die Angaben über die Häufigkeit der ektopischen Graviditäten in der Literatur variieren sehr Es werden Zahlen von etwa 1 ‰ – etwa 3 % angegeben (Seitz und Amreich, 1955) An unserer Klinik ist in den letzten Jahren die Häufigkeit der ektopischen Gravidität etwa 1 % gewesen (bezogen auf die Anzahl der Geburten)

Bei der Operation von Tubargraviditäten können sich folgende Möglichkeiten für das operative Vorgehen ergeben Expressio oder (und) excochleatio ovi, sectio tubae (salpingotomia) resectio tubae mit oder ohne eventuelle Anastomose (nähen oder kleben) und schließlich salpingektomia. – In Lehrbüchern und Handbüchern wird leider immer noch meistens die Exstirpation der befallenen Tube empfohlen (z.B Te Linde, 1946 Beacham, 1950 Seitz und Amreich, 1955 Martius, 1960 Novak und Jones, 1961) –

Nach einer einfachen expressio ovi mit nachfolgender sehr vorsichtiger Kürettage kann es nicht nur wie einige Gynäkologen meinen, zu einer Ausbuchtung (siehe Abb 5) sondern auch, abgesehen natürlich von einem wünschenswerten Verlauf zu einer Okklusion des Lumens kommen. Letzteres kann ebenfalls nach einer einfachen und unkomplizierten Salpingotomie (sectio tubae) mit nachfolgender Naht der Inzisionsöffnung eintreten. Das Röntgenbild (siehe Abb 6) und der makroskopische Primär befund im Laparoskop können im Falle einer sectio tubae aber auch ganz normal sein und erst die Methylenblauinstillation während der Laparoskopie kann in der Lage sein, einen groben Defekt zu enthüllen (siehe Abb 7 Swolin, K., Acta obstet. gynec scand. 46 204, 1967 diese Patientin bekam knapp ein Jahr nach der ersten Tubargravidität eine zweite in derselben Tube) Sogar nach einer exakten Naht einer Resektionsstelle mit mehreren Nähten kann es zu einer Diastase der Resektionskanten mit fehlender Passage durch den lateralen Teil kommen (siehe Abb. 7)

Selbst wenn bisher nicht erwiesen ist, dass eine Resektion eines Teils der Tube ohne nachfolgende Naht bessere Resultate zeitigt als eine exakte Naht der Resektionsstelle so bietet sie gewisse Vorteile. Einmal ist es die Auffassung des Verfassers

teils nach der Röntgenuntersuchung des vorhergehenden Tages die Durchgängigkeit erschwert haben. In keinem der hier beschriebenen Fälle wurde jedoch im Laparoskop eine entzündliche Reaktion der Fimbrien auf die vorausgegangene Hysterosalpingographie beobachtet. –

Eine Diskrepanz zwischen *röntgenologischem und laparoskopischem* Befund erlaubt vielleicht auch, mitunter gewisse Schlüsse auf den funktionellen Zustand der Tube ziehen zu können. Auf keinen Fall ist es jedoch berechtigt, hieraus zu folgern, dass die eine Methode der anderen überlegen sei. Beide haben ihre teilweise voneinander abweichenden Indikationen, Vorzüge und Grenzen.

Betrachtet man die verschiedenen Fakta der Tabelle I, so findet man keinen bindenden Beweis für einen bedeutenden Einfluss der Resektionsstelle auf eine gute Restitution. Es ergibt sich jedoch der Eindruck, dass es vielleicht günstiger ist, eine Resektionsstelle im mittleren Drittel zu haben. Eine Schwellung oder ödematöse Auftreibung der Resektionskanten sowie eine instrumentelle Blutstillung an diesen während der Operation scheinen nicht die Prognose für eine gute Restitution zu verschlechtern. Eine zu grosse Differenz der Lumenweite der Resektionskanten (Fall Nr. 4) und ein nicht gerader, auf die gegenüberliegende Resektionskante gerichteter Verlauf der Endosalpinx (Fall Nr. 2 und 7) sind vielleicht ebenso wie eine zu grosse Resektionslänge (Fall Nr. 4 *und 13) ungünstig für gute Resultate.* Ein Einfluss der intraperitonealen Hydrocortisonapplikation auf die Durchgängigkeit der resezierten und zusammengewachsenen Tuben lässt sich nicht feststellen. Die beiden Fälle mit der makroskopischen Diastase finden sich jedoch in der Gruppe der mit Glukokortikoid behandelten Frauen. Die Betrachtung der Befunde der mikroskopisch untersuchten Präparate erlaubt keinen bindenden Schluss in einer bestimmten Richtung.

Fragt man sich, welchen praktischen Nutzen man aus den im vorstehenden zitierten Untersuchungen und Resultaten ziehen kann, so ergeben sich für den operierenden Gynäkologen zwei Situationen für eine mögliche Anwendung in der Praxis. Dies ist bei der Operation von Eileiterschwangerschaften und bei Tubarplastiken. Die *Sterilitätsoperationen – eigentlich sollte man*

Zusammenfassung

Es werden Querresektionen an graviden Eileitern beschrieben, bei denen die restierenden Tubenstümpfe ohne Naht belassen wurden.

Von 14 auf diese Weise operierten Patientinnen konnten 13 mit Photolaparoskopie und Hysterosalpingographie nachunter sucht werden. Nur in 2 Fällen zeigte sich bei der laparoskopischen Inspektion eine Diastase an der Resektionsstelle bei einem drit ten Fall verhinderten Verwachsungen an der Resektionsstelle eine Betrachtung derselben. Insgesamt in 6 wahrscheinlich in 7 der 13 nachuntersuchten Fälle fand sich eine laparoskopisch oder röntgenologisch nachweisbare Passage durch die Fimbrien der resezierten Tube. Bei der Laparoskopie zeigte sich in 5 Fällen eine sichere und in einem sechsten Fall eine wahrscheinliche Passage der instillierten Blaulösung. Das Hysterosalpingogramm ergab in 4 Fällen einen einwandfreien Beweis für die Passage, während bei 2 weiteren Patientinnen das Röntgenbild nicht als beweisend gewertet werden konnte. Operationen und Nachkontrollen waren frei von Komplikationen.

Die Diskrepanz zwischen Röntgenbild und Laparoskopiebefund wird diskutiert. Der Wert einer konservativen Therapie gemäss der oben beschriebenen Methode wird hervorgehoben und zur Diskussion gestellt.

Der Medizinischen Fakultät der Universität in Göteborg danke ich für die finanzielle Unterstützung dieser Arbeit. Meinem verehrten Chef, Professor Sam Brody möchte ich an dieser Stelle meinen tief empfundenen Dank aussprechen für alle Unterstützung bei der Durchführung der beschriebenen Studien. Meinen Kollegen, Dr Sture Sturm und Dr Magnus Rosencrantz, von der Röntgenabteilung II Sahlgrenska sjukhuset in Göteborg, bin ich zu Dank verpflichtet für die freundliche Hilf bei der Auswertung und Diskussion der Röntgenbilder. Dozent Ingmar Wickbom danke ich für die freundliche Zurverfügungstellung von Röntgenbildern der Röntgenabteilung II.

SUMMARY

Transverse resection of the fallopian tube in cases of tubal pregnancy has been reported. No suturing of the tubal segments was performed they were left free. The mesosalpinx was

gestützt auf Erfahrungen am Material der Klinik, und anderer Autoren (Palmer 1960 Hayashi, 1966 Trnka und Trnková, 1966) dass Fertilitätsoperationen oder Manipulationen an den Eileitern in der Absicht die Fertilität zu fördern, während sogenannter akuter Operationen schlechte Resultate ergeben. Zum anderen ist es sicher oft so dass der eine akute Operation einer Tubargravidität ausführende diensthabende Arzt sehr wenig Zeit für subtile und zeitraubende Operationstechniken an der affizierten Tube hat. Mitunter kann auch der Zustand *der Patientin zu schlecht sein um eine langwierige Operation zu* erlauben. Und zuletzt noch ein Punkt der falls es das Aussehen und der Zustand der Tube erlaubt für eine Resektion ohne nachfolgende Naht spricht. Sollte keine Restitution mit guter Passage auf eine solche Operation erfolgen so ist wenigstens auf diese Art und Weise so viel wie möglich von der Tube erhalten geblieben um die Chancen einer eventuellen zu einem späteren Zeitpunkt durchzuführenden Tubarplastik zu vergrössern. Alle diese Gesichtspunkte gelten natürlich nur wenn man eine gegenüber den meisten Lehrbüchern mehr konservative Einstellung hat und so viel wie möglich von der Tube bewahren will. Es hat jedoch den Anschein als ob die Zeit der „Tubenräuber (Sellheim) von einer Zeit mit einer mehr konservativen den Eileiter möglichst bewahrenden Einstellung abgelöst wird (Prochownik, 1895 Sellheim, 1928 Caffier 1942 Stromme 1953 Järvinen, 1954 Tompkins 1956 Jarvinen und Kinnunen 1957 Aleksandrov 1959 Bertocchi und Rossetti, 1959 Chuberre und Chuberre Durey 1959 Lambillon *et al* 1959 Ženíšek und Stehlíková, 1959 Moreaux und Chartier 1960 Palmer 1960 Rosenblum *et al* 1960 Ploman und Wicksell, 1960 Schenk 1960 Vehaskari 1960 Bakke 1961 Burger 1961 Cagliero 1961 Jarvinen 1961 Reist, 1961 Sjövall, 1961 Bettzieche 1962 Ingersoll 1962 Mintz 1962 Stromme *et al* 1962 v Mikulicz Radecki 1963 Abrams und Farell, 1964 Bass 1964 Isaacs und O Connor 1964 Shordania *et al* 1964 Skulj *et al* 1964 Selmeci, 1965)

Zusammenfassung

Es werden Querresektionen an graviden Eileitern beschrieben bei denen die restierenden Tubenstümpfe ohne Naht belassen wurden

Von 14 auf diese Weise operierten Patientinnen konnten 13 mit Photolaparoskopie und Hysterosalpingographie nachunter sucht werden. Nur in 2 Fällen zeigte sich bei der laparoskopischen Inspektion eine Diastase an der Resektionsstelle, bei einem drit ten Fall verhinderten Verwachsungen an der Resektionsstelle eine Betrachtung derselben. Insgesamt in 6 wahrscheinlich in 7 der 13 nachuntersuchten Fälle fand sich eine laparoskopisch oder röntgenologisch nachweisbare Passage durch die Fimbrien der resezierten Tube. Bei der Laparoskopie zeigte sich in 5 Fällen eine sichere und in einem sechsten Fall eine wahrscheinliche Passage der instillierten Blaulösung. Das Hysterosalpingogramm ergab in 4 Fällen einen einwandfreien Beweis für die Passage, während bei 2 weiteren Patientinnen das Röntgenbild nicht als beweisend gewertet werden konnte. Operationen und Nachkontrollen waren frei von Komplikationen.

Die Diskrepanz zwischen Röntgenbild und Laparoskopiebefund wird diskutiert. Der Wert einer konservativen Therapie gemäss der oben beschriebenen Methode wird hervorgehoben und zur Diskussion gestellt.

Der Medizinischen Fakultät der Universität in Göteborg danke ich für die finanzielle Unterstützung dieser Arbeit. Meinem verehrten Chef, Professor Sam Brody möchte ich an dieser Stelle meinen tief empfundenen Dank aussprechen für alle Unterstützung bei der Durchführung der beschriebenen Studien. Meinen Kollegen, Dr. Sture Stättin und Dr Magnus Rosencrantz, von der Röntgenabteilung II Sahlgrenska sjukhuset in Göteborg, bin ich zu Dank verpflichtet für die freundliche Hilf bei der Auswertung und Diskussion der Röntgenbilder. Dozent Ingmar Wickbom danke ich für die freundliche Zurverfügungstellung von Röntgenbildern der Röntgenabteilung II.

SUMMARY

Transverse resection of the fallopian tube in cases of tubal pregnancy has been reported. No suturing of the tubal segments was performed they were left free. The mesosalpinx was

adapted with one or more single stitches Of the 14 patients operated on in this way 13 could be controlled by photolaparoscopy and hysterosalpingography three or more months after the operation

True diastasis was found at laparoscopy in only 2 patients in a third adhesions at the site of the resection prevented inspection A passage through the fimbriated ends of the resected tubes could be shown by means of laparoscopy or hysterosalpingography in 6 probably in 7 patients The methylene blue instillation at laparoscopy gave evidence of passage in 5 patients and indicated probable passage in a sixth The roentgenograms demonstrated free passage in 4 cases but in 2 other patients there were strong but not conclusive indications of passage No complications followed the operations or the control examinations

The difference between the laparoscopic and roentgenological findings is discussed.

The value of a conservative treatment of a tubal pregnancy by the described method is pointed out and left open for general consideration

LITERATURVERZEICHNIS

Abrams J und *Farell D* Obstet. and Gynec. 24 281 1964
Aleksandrov E. Akush. I Ginek., 35 68 mar apr 1959
Bakke O T norske lægeforen., 8 989 1961
Bass S Schweiz. med. Wschr 94 1297 1964
Beacham W Progress in Gynecology 2 365 New York 1950
Bertocchi F und *Rossetti O* Quad. Clin. ostet. gin 14 759 1959
Bettzieche H Zbl. Gynäk. 84 38 1962
Burger K. Geburtsh. u. Frauenheilk. 21 633 1961
Caffier P Arch. Gynäk. 173 281 1942
Cagliero L Min. ginec. 13 10 1961
Chuberre B und *Chuberre-Durey A* Bull. Féd Soc. Gynéc Obstét. franç., 11 439 1959
Hayashi M pers. Mitteilung, 1966
Ingersoll F Clin. Obstet. and Gynec 5 853 1962
Isaacs J und *O'Connor J* Obstet. and Gynec. 23 187 1964
Järvinen P Ann. Chir Gynaec. Fenniae 43 185 1954
Järvinen P und *Kinnunen O* Int. J Fertil 2 131 1957
Järvinen P Int. J Fertil 6 269 1961
Lambillon J *Mettens J* und *Kabers A.* Int. J Fertil. 4 330 1959

Martius H Die gynäkologischen Operationen, 8. Aufl. Stuttgart, 1960
Mayer A. Beitr zur Fertil. und Steril., Beilageheft Z. Geburtsh., Bd. 152, Vol. 2 S 59, 1959
Mikulicz-Radecki F Gynäkologische Operationen, Leipzig, 963
Mintz M. Gynéc. et Obstét., 6 365, 962
Moreaux J und Chertier M Presse méd., 68 2131 1960
Novak, E. und Jones G Novak's Textbook of Gynecology 6th Ed., Baltimore 96
Palmer R Rev Prat. (Paris) 353 1960
Plomen L. und Wicksell F Acta obstet. gynec. scand., 39, 43, 960
Prochownik L Arch. Gynäk 49, 77 895
Reitz A zit Burger 196
Rosenblum J Dowling, R. und Barnes A. Amer J Obstet. Gynec., 80 274 960
Schenk G Zbl. Gynäk 82, 863, 960
Seitz L und Amreich A. Biologie und Pathologie des Weibes, Bd. 9, Berlin–Innsbruck–München–Wien, 955
Sellheim H Med. Klin 24 1736 1928
zit Mayer 1959
Solnerci E. Orv Hetil., 06 1806 965
Shordania J Gotsiridze O und Gwaradzishvili A., Zbl Gynäk. 86 824, 964
Sjövall A pers. Mitteilung, 96
Skalj V Perbic Z Stolfjkovic C Bacic C und Drazancic A. Fert. and Steril 5, 634 1964
Stamm S pers Mitteilung, 966
Stromme W Obstet. and Gynec., 1 472, 953
Stromme W McKelvey J und Adkins C Obstet. and Gynec 19, 294 962
Swolin K. Acta obstet. gynec. scand 45, 43 966
Acta obstet gynec scand 46 204, 967
Swolin K und Rosencrantz M. In Vorbereitung
T Linde R Operative Gynecology Philadelphia, London, Montreal, 1948
Tompkins E Fertil. and Steril 7 448 958
Truka V und Trnkova M 5 Weltkongr Fertil Steril Stockholm, 966
Vehaskari A Acta obstet. gynec scand 30, Suppl. 3, 960
Weinman A Radiology 56 04 951
Zenisek L und Stehlikova J Cs Gynek 24, 703 1959

Am Okt 966 erhalten

adapted with one or more single stitches. Of the 14 patients operated on in this way 13 could be controlled by photolaparoscopy and hysterosalpingography three or more months after the operation

True diastasis was found at laparoscopy in only 2 patients, in a third adhesions at the site of the resection prevented inspection A passage through the fimbriated ends of the resected tubes could be shown by means of laparoscopy or hysterosalpingography in 6 probably in 7 patients. The methylene blue instillation at laparoscopy gave evidence of passage in 5 patients and indicated probable passage in a sixth. The roentgenograms demonstrated free passage in 4 cases but in 2 other patients there were strong but not conclusive indications of passage. No complications followed the operations or the control examinations.

The difference between the laparoscopic and roentgenological findings is discussed.

The value of a conservative treatment of a tubal pregnancy by the described method is pointed out and left open for general consideration

LITERATURVERZEICHNIS

Abrams J und *Farell D* Obstet. and Gynec. 24 -81 1964
Aleksandrov E, Akush. i Ginek., 35 68 mar-apr 959
Babbe O., T norske lægeforen 8 989 1961
Bass S. Schweiz. med. Wschr 94 1297 1964
Beacham W Progress in Gynecology 2 365 New York, 1950
Berrocchi F und *Rossetti O* Quad. Clin. ostet. gin. 14 759 1959
Bettzieche H Zbl. Gynäk., 84 38 1962
Burger K. Geburtsh u. Frauenheilk. 21 633 1961
Caffier P Arch. Gynäk. 173 -61 194
Cagliero L. Min. ginec. 13 10 1961
Chuberre B. und *Chuberre-Durey A.* Bull. Féd. Soc Gynéc Obstét. franc 11 439 1959
Hayashi M pers. Mitteilung, 1966
Ingersoll F Clin. Obstet. and Gynec 5 853 1962
Isaacs J und *O Connor J* Obstet. and Gynec., 23 187 1964
Järvinen P Ann. Chir Gynaec. Fenniae, 43 185 1954
Jarvinen P und *Kinnunen O* Int. J. Fertil., 2 131 1957
Jarvinen P Int. J Fertil 6 269 1961
Lambillon J., *Mettens J* und *Kabare A.* Int. J Fertil. 4 330 1959

Martius H Die gynäkologischen Operationen, 8 Aufl., Stuttgart, 1960
Mayer A. Beitr zur Fertil. und Steril., Beilageheft Z. Geburtsh., Bd. 152, Vol. S. 59, 959
Münchner-Radecki F Gynäkologische Operationen Leipzig, 1963
Moerz M Gynéc. et Obstét., 61 385, 1962
Moreaux J und Chartier M., Presse méd., 68 2 31 1960
Novak E. und Jones, G Novak's Textbook of Gynecology 6th Ed Baltimore, 96
Palmer R. Rev Prat. (Paris) 0 3531 960
Plomon L. und Wicksell F Acta obstet. gynec. scand 39, 143, 1960
Prochownik, L., Arch. Gynäk., 40, 177 895
Reitz A zit Berger 96
Rosenblum J Doering, R. und Barnes, A. Amer J Obstet. Gynec., 80 174 960
Schenk G Zbl. Gynäk 82, 863, 1960
Seitz L. und Amreich A. Biologie und Pathologie des Weibes Bd. 9, Berlin-Innsbruck-München-Wien 1955
Sellheim H Med. Klin., 24 1738 1928
zit Mayer 1959
Salmeri E. Orv Hetil., 06 1806 1965
Shordania J Gottlridse O und Gwerdtsitheli A. Zbl Gynäk. 86 814 964
Sjövall A pers. Mitteilung, 96
Skulj V Parlic Z., Stoffjkovic C Bacic G und Drezancic A Fert. and Steril., 5 634 1964
Stetten S pers Mitteilung, 1966
Stromme W Obstet. and Gynec., 472, 1953
Stromme W McKelvey J und Adams C. Obstet. and Gynec., 9, 294 962
Swolin K. Acta obstet. gynec scand 45, 451 966
Acta obstet gynec. scand 46 204, 967
Swolin K und Rosencrantz M. in Vorbereitung
T Linde R Operative Gynecology Philadelphia, London, Montreal, 1948
Tompkins E Fertil. and Steril 7 448 956
Trnka V und Trnková, M 5 Weltkongr Fertil Steril Stockholm, 966
Velhaubert, A Acta obstet gynec scand 39, Suppl. 3, 960
Weissman A Radiology 56 104 95
Zemlek L und Steklhková J., C Gynek., 24 703, 959

Am Okt 1966 erhalten

Swolin, Kurt, Acta obst. et gynec. scandinav. 46, 234, 1967

Aus der Frauenklinik (Professor Sam Brody) der Universität in Göteborg, Schweden

50 FERTILITÄTSOPERATIONEN

Teil I Literatur und Methodik

VON

KURT SWOLIN

„Die ersten 50 waren nur als Pionierarbeit, als ein Wegbahnen von *experimentellem Charakter zu betrachten mit einem hohen* Prozentsatz von postoperativen Verschlussen Diese Worte stammen aus einem Vortrag eines unserer erfahrensten Experten, ja, man darf wohl sagen einem der Altmeister auf dem Gebiet der Fertilitätsoperationen (Shirodkar 1961)

Die folgende Arbeit ist ein Bericht über die ersten 50 serienmässig erfassten vom Verfasser ausgeführten Fertilitätsoperationen mit den dazugehörigen Vor und Nachuntersuchungen.

Die in Tabelle I dargestellten Ziffern und Fakta geben einen kurzen Einblick in die zum Thema gehörige Literatur und somit dem Leser die Möglichkeit, die in dieser Arbeit angeschnittenen Probleme und deren Hintergründe besser verstehen zu können. Die Angaben die Arbeitsmethoden, die Art der Berichterstattung und die Resultate variieren in einem so hohen Grade (siehe Tab I) dass es ein schwieriges Unterfangen – man möchte sagen bei dem augenblicklichen Stand der Dinge eine unmögliche Auf gabe – ist, einen auch nur einigermassen gerechten Vergleich ziehen zu wollen Es fehlen Arbeiten mit ausführlicher Wieder gabe von prä- und postoperativen Untersuchungen, – falls uber haupt solche in grösserem Umfang gemacht worden sind – um eine exakte wissenschaftliche Beurteilung des veröffentlichten Materials zu ermöglichen Es gibt nur wenige Arbeiten die ver stehen lassen dass die Operationen von ein und demselben Operateur ausgeführt worden sind, was für die Beurteilung der Ope-

rationstechnik nicht ohne Bedeutung sein dürfte. Selten werden Resultate so detailliert publiziert, dass man die Anzahl von Graviditäten, Geburten, Aborten und ektopischen Graviditäten sehen oder zumindest errechnen kann. Mitunter wird zum Beispiel von Erfolgen gesprochen, ohne dass der Leser immer weiss, ob hier mit Passage Graviditäten oder Geburten gemeint sind. – Operationstechnisch gesehen ist schon die Passage ein Erfolg, im Hinblick auf die Behandlung der Sterilität ist dies jedoch erst das lebende Kind. Bei der Beurteilung der Passage ist es sehr wichtig zu wissen wann und mit welcher Methode die Passage geprüft wird. – Die Zahlen der frühen oder späten Passageprüfung unterscheiden sich erheblich (siehe z.B. Rust, 1963 Hanton et al 1964) – Von ausschlaggebender Bedeutung ist ferner zu wissen ob die Operation auf beiden Seiten oder an der einzigen übriggebliebenden (oder -gebliebenen) Tube ausgeführt wurde. Weiter ist die Frage der Auswahl der Fälle von grosser Wichtigkeit. Werden nur „leichte Fälle" operiert, so ist es klar dass gute Resultate publiziert werden können – Nach Hayashi (1966) sind z.B die Resultate von Salpingostomien falls man die Operationen in 3 Schweregrade einteilt, rund 50% in Gruppe I, rund 15% in Gruppe II und nur 0–5% in Gruppe III. – Nur wenige Verfasser teilen die Fälle mit, bei denen erst wegen einer Sterilität zu einer Laparotomie geschritten wurde, bei denen jedoch dann – z.B. wegen der Schwere der Verwachsungen – Abstand von einer Fertilitätsoperation genommen wurde. Diese schweren Fälle scheinen selten in die Zahl der operierten Fälle aufgenommen zu werden und verbessern auf diese Weise natürlich die publizierten Resultate Die Ursachen für die erhebliche Differenz der veröffentlichten Resultate (siehe Tab. I) kann kaum nur in der Verschiedenartigkeit der Operationstechniken liegen

Erst die Publikation von mehr Arbeiten mit detaillierten Angaben über sowohl Vor und Nachuntersuchungen als auch über die einzelnen Fälle für sich schafft Vergleichsmöglichkeiten und hiermit ein grosses statistisch zu bearbeitendes Operationsmaterial. Nur auf diese Art und Weise werden für die Zukunft gute Möglichkeiten geschaffen eine ausgedehnte und exakte klinische Forschung auf dem Gebiete der Fertilitätsoperationen betreiben zu können.

Tabelle 1 *Resultate von Fertilitätsoperationen*

Verfasser		Operation (Anzahl, Typ Material, Zeit etc)	Passage %	Gravidität %	Geburt %	Abort %	Ektop. Grav %
Athanassiu	(1944)	63 Tubenverschlussoperationen (sehr wahrscheinlich nur Salpingolysen aus der Klinik Martius 10 Jahre)			27		
Athanassiu	(1944)	12 Fälle mit doppelseitigem Verschluss (ampullär oder isthmisch)		0			
Bergman	(1963)	22 Tubarplastiken (1958—1961)	50	0			
Bohm und Englund	(1946)	50 Salpingostomien (1931—1942 26 doppelseitige 24 einseitige bei der einzigen Tube)		10(ev 12)	2	2	6(ev 8)
Bunster	(1951)	Zusammenstellung aus der Weltliteratur salpingolysis			20		
		Zusammenstellung aus der Weltliteratur salpingostomia			7		
		Zusammenstellung aus der Weltliteratur implantatio tubae			25,5		
Chalier	(195C)	71 ,S lpingotomie linéaire					
Comninos	(1954)	37 nachuntersuchte Salpingost mien (von 148 Op)	37,5	15			
Eguchi	(1959)	81 Tubarplastiken (Op Material von 2 J h en)		16		5,4	2,7
Grant und Mackey	(1955)	122 Tubarplastiken		18,3	9 8	2 4	C 1
Grant und Mack y	(1962 1963)	38 S lpingost mien	67,2	24 6			
		165 Tubarpla tiken	60,5	10,5	5,2	2 4	1 6
Green A myt ge	(1936)	25 S lpi gost mie		?2 5		2 6	2 6
							4)

Green Armitage	(1959)	43 Tubenimplantationen		40 46			2
Green Armitage	(1960)	Salpingostomie (Anzahl?)		6 6	4 4	0,98	1,2
Greenhill	(1937)	818 Tuberplastiken (711 Salpingostomien und 107 Tubenimplantationen, per Brief Fragebogen an amerik. Gynäkologen, 107 Antworten)		19 1	15 1		(2,9)
Greenhill	(1956)	2113 Tuberplastiken Zusammenstellung aus Weltliteratur und pers. Mitteilungen		24	16	6,6	1,3
Hanton et alii	(1964)	75 Tuberplastiken (1945—1962) Passage geprüft nach 1 Mon.—10 Jahre (bei 49 Pat.)	54,9				
		Passage vor der Entlassung aus dem Krankenhaus geprüft	74,1	18,4	3,1	12,4	3,1
		32 Salpingostomien (1945—1962) Passage geprüft nach 1 Mon.—10 Jahre (bei 22 Pat.)	50				
		Passage vor der Entlassung aus dem Krankenhaus geprüft	70,9	18,5			5,5
Hayashi	(1961)	108 Tuberplastiken		17			
Hayashi	(1966)	287 Tuberplastiken			33		
Holtz	(1951)	24 Tubenimplantationen			15		
		27 Salpingostomien			8,6		
Kustner	(1936)	93 Salpingostomien (Sammelstatistik)		15			
Leblanc	(1959)	296 Salpingostomien (Palmers Material 1942—1956)		35,3	20,3	5 7	9,2
Mackey	(1966)	88 Salpingolysen		14,3	11,1		3,2
		63 Salpingostomien			28		
Mahomla	(1958)	25 Tubo-uterine Implantationen (Södersjukhuset Stockholm, verschiedene Operateure)					

Tabelle 1 *Resultate von Fertilitätsoperationen*

Verfasser		Operation (Anzahl, Typ, Material, Zeit etc.)	Passage %	Gravidität %	Geburt %	Abort %	Ektop. Grav. %
...anescu	(1944)	63 Tubenverschlussoperationen (sehr wahrscheinlich nur Salpingolysen aus der Klinik Martius 10 Jahre)			27		
...anascu	(1944)	12 Fälle mit doppelseitigem Verschluss (ampullär oder isthmisch)		0			
...gman	(1963)	22 Tubarplastiken (1958—1961)	50	0			
...m und Englund	(1946)	50 Salpingostomien (1931—1942, 26 doppelseitige 24 einseitige bei der einzigen Tube)		10(ev 12)	2	2	6(ev 8)
...ster	(1951)	Zusammenstellung aus der Weltliteratur salpingolysis			20		
		Zusammenstellung aus der Weltliteratur salpingostomia			7		
		Zusammenstellung aus der Weltliteratur implantatio tubae			25,5		
...lter	(1956)	71 „Salpingotomie linéaire"		15			
...nnnos	(1954)	37 nachuntersuchte Salpingostomien (von 148 Op.)	37,5	16		5,4	2,7
...chi	(1959)	81 Tubarplastiken (Op. Material von 2 Jahren)		18,3	9 8	2 4	6,1
...nt und Mackey	(1955)	122 Tubarplastiken	67,2	24 6		2,4	1 6
...nt und Mackey	(1962, 1963)	38 Salpingostomien	60,5	10,5	5,2	2,6	2,8
		165 Tubarplastiken		22 5			4 9
...een-Armytag	(1936)	25 Salpi[illegible]gostomi[illegible]n		19			

		Späte Passageprüfung mit HSG bei	18,1				
		11 von 29 Pat	18	0			
...ager	(1964)	11 reine Salpingostomien		21			
...erdaus ov	(1956)	288 Tubenplastiken	90	35			5
...hirodkar	(1960)	140 Tubenimplantationen	60 (nach 1 Jahr)		20		
...hirodkar	(1966)	350 Tubenimplantationen (Material von 20 Jhr.)	80 (nach 1 Jahr)		35		
		100 Tubenimplantationen („clean cases")			16,6		
...iegler und Hellmann	(1956)	2285 Tubenplastiken (Rundfrage amerik. Gynäkologen. Resultate von 84 Spezialisten mit mehr als 10 Tubenplastiken)		20,7	15,8	2,4	2,5
		891 Salpingostomien		8	6 (+ 1 grs. m. III)		
Siegler und Hellmann	(1963)	50 Tubenplastiken (eigene Fälle 1953—1962)		11 1	5 6		
		18 Tubenplastiken („pure op.")	39 (3—16 Mon.)				
		8 bilat. ampulläre Salpingostomien		0			
Svanberg	(1960)	20 Salpingoplastiken (mit Hilf von Saktosalpinx-Fistel zwischen Ovarium und Uterus)		1 Pat. hatte 5 Graviditäten, darunter 3 Lebendgeburten	23		
Vara	(1959)	186 Tubenplastiken ohne Plastikprothese (1947—1957)			5		
		39 Salpingostomien ohne Plastikprothese (1947—1957)			19		
		63 Tubenplastiken mit Plastikprothese (1947—1957)					

Tabelle I (Forts.)

Verfasser		Operation (Anzahl, Typ, Material, Zeit etc.)	Passage %	Gravidität %	Geburt %	Abort %	Ektop. Grav. %
Martin	(1895)	65 Salpingostomatomien (hatte 2 Todesfalle)		3 1			
Martius	(1951)	65 Tubenverschlussoperationen, bilaterale (Privatklinik Martius 1945—1950 sehr wahrscheinlich nur Salpingolysen)		53			
Murray	(1956)	56 Salpingostomien					
Özaras	(1967)	300 Fertil-Op (Karolinska sjukhuset Stockholm, Nachforschungen per Brief über Op 1940—1964)	42,8	17,8 10,3	5 7	3	1 7
Palmer und Proust	(1953)	40 ampullo-uterine Implantationen („des cas purs") Passage kontrolliert mit Insufflation (nur 19 Fälle mit HSG)	75	39,5			7,5
Palmer	(1966b)	363 Salpingostomien (Palmers eigene Fälle 1942—1963)	56	24			
Poradovský	(1959)	36 Tuberplastiken					5,7
Pous Puigmacia	(1960)	3018 Fertil.-Op (Zusammenstellung aus Weltliteratur)	36	14 22,6	10		
		559 Salpingostomien mit Plastikprothese	36,03	17,53			2 68
		1377 Salpingostomien ohne Plastikprothese	54 01	13,58			3,75
Rio et ali	(1964)	18 reine Salpl gost mien (1958—1963 mit Fallbeschreibung)		5,8	0	5,8	1,37
Rust	(1963)	29 Salpingostomien früh Passageprüfung, 10 + 14 T g	48,3				

Methodik

Präoperative Untersuchung

An der Universitätsfrauenklinik in Göteborg versuchen wir seit 1961 alle präsumptiven Fertilitätsoperationen rein routinemässig nach einem für diese Zwecke aufgestellten Schema zu untersuchen. Die einzelnen Untersuchungsmethoden sind an sich nichts Neues, da die Methodiken jedoch von Klinik zu Klinik mitunter bedeutend differieren soll in dieser Arbeit ausführlich auf die einzelnen Untersuchungsmethoden eingegangen werden Das Schema für die präoperativen Ermittlungen enthält folgende Untersuchungen Sperma-Analyse Basaltemperaturkurve Menstruationsblutuntersuchung, Lungenröntgen, Hysterosalpingographie Postcoitaltest, Endometriumbiopsie, Laparoskopie und eventuell Hydropertubation. Die Reihenfolge der Untersuchungen braucht nicht zwangsläufig dem aufgestellten Schema zu folgen sondern ist dem Belieben des behandelnden Kollegen überlassen

Zu Anfang der in dieser Arbeit angeführten Fertilitätsoperationsserie ist ein Grossteil der Voruntersuchungen die vorgenommen werden durften vom Verfasser selbst durchgeführt worden später haben aber ebenfalls die Kollegen der Klinik in grösserem Ausmasse an den präoperativen Untersuchungen teilgenommen (das Einlegen der Hysterosalpingographiekanüle wird seit 1963 von den Röntgenologen der Röntgenabteilung II selbst ausgeführt)

Aus verschiedenen Gründen war es, besonders zu Anfang der geplanten Fertilitätsoperationsserie nicht immer möglich die gewünschte komplette Untersuchung durchzuführen und der Verfasser war mehr oder weniger gezwungen, auch nicht ganz vollständig voruntersuchte Fälle zu operieren, um diese nicht für den Aufbau eines Operationsmaterials zu verlieren.

Die Spermauntersuchung wird gerne an den Anfang aller Untersuchungen gestellt und geschieht in dem Routinelaboratorium unserer Klinik. In Schweden haben wir sehr selten Schwierigkeiten, die Männer zur Mitarbeit zu gewinnen Zur Zeit wird an unserer Klinik auf folgende Details bei der Spermauntersuchung eingegangen Volumen des Ejakulats, Anzahl der Spermien per

Tabelle I. (Forts.)

Verfasser		Operation (Anzahl, Typ, Material, Zeit etc.)	Passage %	Gravidität %	Geburt %	Abort %	ektop. Grav. %
		28 Salpingostomien mit Plastikprothese (1947—1957)			18		
Vara	(1965)	119 Tubarplastiken ohne Plastikprothese (1957—1963)			26		
		18 Salpingostomien ohne Plastikprothese (1957—1963)			11		
		200 Tubarplastiken mit Plastikprothese (1957—1963)			25		
		109 Salpingostomien mit Plastikprothese (1957—1963)			18		
Westman	(1951)	453 abdominale Fertil.—Op Karolinska sjukhuset Stockholm (1936—1945)		20		nicht genannt aber schätzungsweise etwa 2,9 % für beide Gruppen	
		140 Salpingostomien		6 4			

Methodik

Präoperative Untersuchung

An der Universitätsfrauenklinik in Göteborg versuchen wir seit 1961 alle präsumptiven Fertilitätsoperationen rein routinemäßig nach einem für diese Zwecke aufgestellten Schema zu untersuchen. Die einzelnen Untersuchungsmethoden sind an sich nichts Neues, da die Methodiken jedoch von Klinik zu Klinik mitunter bedeutend differieren, soll in dieser Arbeit ausführlich auf die einzelnen Untersuchungsmethoden eingegangen werden. Das Schema für die präoperativen Ermittlungen enthält folgende Untersuchungen: Sperma-Analyse, Basaltemperaturkurve, Menstruationsblutuntersuchung, Lungenröntgen, Hysterosalpingographie, Postcoitaltest, Endometriumbiopsie, Laparoskopie und eventuell Hydropertubation. Die Reihenfolge der Untersuchungen braucht nicht zwangsläufig dem aufgestellten Schema zu folgen, sondern ist dem Belieben des behandelnden Kollegen überlassen.

Zu Anfang der in dieser Arbeit angeführten Fertilitätsoperationsserie ist ein Grossteil der Voruntersuchungen, die vorgenommen werden durften, vom Verfasser selbst durchgeführt worden, später haben aber ebenfalls die Kollegen der Klinik in grösserem Ausmasse an den präoperativen Untersuchungen teilgenommen (das Einlegen der Hysterosalpingographiekanüle wird seit 1963 von den Röntgenologen der Röntgenabteilung II selbst ausgeführt).

Aus verschiedenen Gründen war es besonders zu Anfang der geplanten Fertilitätsoperationsserie nicht immer möglich, die gewünschte komplette Untersuchung durchzuführen und der Verfasser war mehr oder weniger gezwungen, auch nicht ganz vollständig voruntersuchte Fälle zu operieren, um diese nicht für den Aufbau eines Operationsmaterials zu verlieren.

Die Spermauntersuchung wird gerne an den Anfang aller Untersuchungen gestellt und geschieht in dem Routinelaboratorium unserer Klinik. In Schweden haben wir sehr selten Schwierigkeiten, die Männer zur Mitarbeit zu gewinnen. Zur Zeit wird an unserer Klinik auf folgende Details bei der Spermauntersuchung eingegangen: Volumen des Ejakulats, Anzahl der Spermien per

ml Motilität und Morphologie. Chemische Analysen wie zum Beispiel die Bestimmung von Fruktose oder Zink, werden noch nicht durchgeführt sind aber geplant. Die Beurteilung der gefundenen Werte der Spermauntersuchung geschieht in Anlehnung an die Richtlinien der American Society for the Study of Sterility (1962)

Wir sehen es gerne dass die Patientinnen die Basaltemperatur während mindestens 3 aufeinanderfolgender Zyklen aufzeichnen.

Gemäss der einschlägigen Literatur und auch persönlicher Mitteilungen aus der letzten Zeit von unter anderen Palmer (1960) Chiara (1966) Hayashi (1966) und Trnka (1966) führt eine unerkannte oder nicht behandelte Tuberkulose praktisch immer zu einem Misserfolg bei Tubarplastiken. Deshalb versuchen wir mit allen Mitteln eine Genitaltuberkulose vor der Operation aufzudecken auch wenn die Zahl der Tuberkulosefälle im Sterilitätsmaterial in Schweden gering ist. Nach Jedberg (1950) ist die Zahl der Tuberkulosefälle in einem 10-jährigen schwedischen Sterilitätsmaterial 2 % (1186 Pat. aus der Stadt Malmö) in Polen z.B sollen 20 % aller Adnexentzündungen tuberkulösen Ursprungs sein (Gromadzki 1960) und nach Laliam (1966) sind etwa 25 % aller Sterilitätsfälle in Algerien bedingt durch eine Tuberkulose. Unsere Routinemethoden eine Tuberkulose im Sterilitätsklientel aufzudecken sind die bakteriologische Untersuchung des Menstruationsblutes die Endometriumbiopsie die Röntgenuntersuchung sowohl der Lungen als auch der Tuben und die Laparoskopie. Bei der Menstruationsblutuntersuchung wird ein Vaginaltampon mit dem ersten Blut und bei der Endometriumbiopsie die Hälfte des Abrasionsmateriales ins bakteriologische Institut geschickt dort wird eine Pathogenitätsbestimmung bei Meerschweinchen und eine Züchtung auf Löwensteinnährböden durchgeführt. In suspekten Fällen werden natürlich mehrmalige Proben und weiter noch eine bakteriologische Untersuchung des Urins durchgeführt.

Die Hysterosalpingographie wird im allgemeinen in der Mitte des Menstruationszyklus vorzugsweise vor der Ovulation durchgeführt. Das seit Jahren benutzte Kontrastmittel ist das wasserlösliche Perjodal H 35 % viskös (AB Pharmacia Uppsala). Seit einigen Jahren wird als Instrumentarium fast ausschliesslich die

kleine durchsichtige Vakuumsaugglocke nach Malmström-Thorén (VUC oder Vacuum-Uterine-Cannula, AB Vacuum-Extraktor Göteborg) benutzt, mit der wir ausgezeichnete Erfahrungen gemacht haben und die für die Patientinnen sehr schonend ist. Ein grosser Teil der Hysterosalpingographien wird ambulant durchgeführt. Patientinnen mit wiederholten Salpingitiden oder kürzlich durchgemachten akuten gynäkologischen Erkrankungen werden jedoch nicht einer ambulanten Behandlung ausgesetzt. Bei einer Tubarokklusion an den Tubenecken erhält die Patientin eine intravenöse Injektion eines Spasmo-Analgeticum, eventuell wird die Untersuchung später nach einer kräftigen Prämedikation wiederholt (z.B. 100 mg Pethidin und 50 mg Lergigan® [Promethazinchlorid AB Recip Stockholm] per inj. intramuscularem, 1 Stunde vor der Untersuchung). Zeigen die Röntgenaufnahmen eine partielle Okklusion oder keine einwandfreie Passage so *ist später eine Hydropertubation indiziert. Die Aussagekraft* einer Hysterosalpingographie ist natürlich begrenzt und wird bei der bisweilen überschätzt. Ihr Wert ist jedoch – auch im Vergleich mit der Laparoskopie – unbestreitbar und kann bis jetzt durch keine andere Methode ersetzt werden. Voraussetzung ist natürlich, dass mögliche Fehlerquellen, z.B. Reflux oder geringer Druck bei Passagehindernis (*vergleiche z.B. Abb. 9 und 10) ausgeschlossen werden.*

Der Postcoitaltest wird mit Hilfe der Basaltemperaturkurve zur Ovulationszeit ausgeführt. Der Wunsch des Verfassers ist es, den Test immer etwa 6–12 Stunden post coitum durchzuführen. – Hierdurch wird einerseits mehr Rücksicht auf das Intimleben des zu untersuchenden Paares genommen und andererseits hat das Cervikalsekret mehr Zeit, eine eventuell negative Beeinflussung der Spermien oder des Ejakulats auszuüben. – Die Beurteilung geschieht, wie auch schon vorher bei der Spermauntersuchung, in Anlehnung an die Richtlinien der American Society for the Study of Sterility (1962). Zur Vereinfachung wird in unkomplizierten Fällen in der Regel nur das Sekret aus der Cervix untersucht, wobei hauptsächlich Wert auf die Spinnbarkeit, die Menge der Spermien und die Beimischung von Leukocyten und Bakterien gelegt wird. Bei den Spermien wird unterschieden zwischen der Anzahl der unbeweglichen, der beweglichen (d.h. der sich auf der

Stelle bewegenden) und der progressiven Spermien. Hierbei wird die mittlere Anzahl von mindestens 5 Gesichtsfeldern berechnet. Die Angabe der Vergrösserung durch den jeweiligen Untersucher ist wichtig (eine einheitliche Auswertung z.B. bei einer Vergrösserung von 200–250 wäre wünschenswert). Die exakte und zeitgerechte Durchführung der Postcoitalteste stösst in der Praxis mitunter auf erhebliche Schwierigkeiten.

Die Endometriumbiopsie sollte als eine prämenstruelle Abrasio durchgeführt werden, wobei die erwünschte Zeit etwa 2–4 Tage vor der Menstruation liegt. Die Endometriumbiopsie wird an unserer Klinik oft als regelrechte Abrasio und selten in Form einer Strichkürettage durchgeführt; sie geschieht oft ambulant. Das Abrasionsmaterial wird sowohl zur histologischen als auch, wie bereits vorher erwähnt, zur bakteriologischen Untersuchung geschickt.

Die Laparoskopie mit gleichzeitiger Prüfung der Passage mit Hilfe einer durch die Cervix instillierten Farblösung (siehe Swolin 1967a, 1967b) ist zu einem festen, wichtigen und nicht mehr fortzudenkenden Bestandteil der Sterilitätsuntersuchung geworden. Sie wird bei uns in Allgemeinnarkose durchgeführt und kann mit Vorteil und ohne Komplikationen mit einer Hysterosalpingographie am Tage vorher oder mit der prämenstruellen Abrasio in derselben Narkose verbunden werden. Während der Laparoskopie sollte immer irgendein intraabdominales Hilfsinstrument, wie z.B. der Stahlstab auf den Abbildungen 2, 5 und 7 der Farbbeilage dieser Arbeit, zur Verfügung stehen, da es sonst fast immer unmöglich ist, eine wirklich exakte und komplette Inspektion des kleinen Beckens und seiner Organe durchzuführen, selbst wenn eine intrauterine Kanüle eine Bewegung des Uterus ermöglicht.

Bei allen Fällen, in denen die Laparoskopie oder vor allem die Hysterosalpingographie eine Passagebehinderung oder nicht ganz einwandfreie Befunde ergeben haben, sollte eine Hydropertubation durchgeführt werden. Die Hydropertubation gibt im Gegensatz zum Hysterosalpingogramm und der Laparoskopie, die mehr den organischen Befund widerspiegeln, mehr ein Bild über den funktionellen Zustand der Tuben und ermöglicht auch eine Objektivierung eines relativen Passagehindernisses und dessen eventuelle

Semm, Kurt, Acta obst. et gynec. scandinav 46, 1967

Abbildung 1—8

Farbbeilage zu der Arbeit 50 Fertilitätsoperationen

Stelle bewegenden) und der progressiven Spermien Hierbei wird die mittlere Anzahl von mindestens 5 Gesichtsfeldern berechnet. Die Angabe der Vergrösserung durch den jeweiligen Untersucher ist wichtig (eine einheitliche Auswertung z.B bei einer Vergrösserung von 200–250 wäre wünschenswert) Die exakte und zeitgerechte Durchführung der Postcoitalteste stösst in der Praxis mitunter auf erhebliche Schwierigkeiten

Die Endometriumbiopsie sollte als eine prämenstruelle Abrasio durchgefuhrt werden wobei die erwünschte Zeit etwa 2–4 Tage *vor der Menstruation* liegt Die *Endometriumbiopsie wird an unserer* Klinik oft als regelrechte Abrasio und selten in Form einer Strichkürettage durchgefuhrt sie geschieht oft ambulant. Das Abrasionsmaterial wird sowohl zur histologischen als auch wie bereits vorher erwahnt zur bakteriologischen Untersuchung geschickt.

Die Laparoskopie mit gleichzeitiger Prüfung der Passage mit Hilfe einer durch die Cervix instillierten Farblösung (siehe Swolin 1967a 1967b) ist zu einem festen wichtigen und nicht mehr fortzudenkenden Bestandteil der Sterilitätsuntersuchung geworden Sie wird bei uns in Allgemeinnarkose durchgeführt und kann mit Vorteil und ohne Komplikationen mit einer Hysterosalpingographie am Tage vorher oder mit der prämenstruellen Abrasio in derselben Narkose verbunden werden Während der Laparoskopie sollte immer irgendein intraabdominales Hilfsinstrument, wie z.B der *Stahlstab auf den Abbildungen 2 5 und 7 der* Farbbeilage dieser Arbeit zur Verfügung stehen da es sonst fast immer unmöglich ist, eine wirklich exakte und komplette Inspektion des kleinen Beckens und seiner Organe durchzuführen selbst wenn eine intrauterine Kanule eine Bewegung des Uterus ermöglicht.

Bei allen Fällen in denen die Laparoskopie oder vor allem die Hysterosalpingographie eine Passagebehinderung oder nicht ganz einwandfreie Befunde ergeben haben sollte eine Hydropertubation durchgeführt werden Die Hydropertubation gibt im Gegensatz zum Hysterosalpingogramm und der Laparoskopie die mehr den organischen Befund widerspiegeln mehr ein Bild über den funktionellen Zustand der Tuben und ermöglicht auch eine Objektivierung eines relativen Passagehindernisses und dessen eventuelle



Abb. 5. Laparoskopie 7 Monate post op., dieselbe Tube wie in Abb. 3 und 4, keine Verwachsungen, sehr schnelle Passage der Methylenblaulösung durch den offenen und frei beweglichen Fimbrientrichter (vergleiche Abb. 12), 10 Monate post op. Eintritt einer intrauterinen Gravidität.

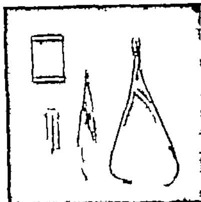


Abb. 6. Zwei wichtige Instrumente, die thermoelektrische Nadelelektrode sowohl für Blutstillung als auch blutarmes Präparieren, und der Mikronadelhalter (vergleiche Grössenverhältnisse mit einer normalen schwedischen Streichholzschachtel ([illegible],2 cm) und dem kleinsten, gebräuchlichen Nadelhalter vom Typ Hirtenbaum (17 cm)).



Abb. 7. Laparoskopie 9 Monate post op. (Pat. Nr. 39), keine Verwachsungen auf der linken Seite (siehe auch Abb. 15 und 17), frei bewegliche Tube und gut formierter Fimbrientrichter nach Salpingostomie und Lösung reichlicher Verwachsungen um Tube und Ovarium.



Abb. 8. Intraoperatives Bild (Pat. aus dem 2. Halbjahr 1969). Salpingostomie links abgeschlossen, bei Beginn der Op. re. und li. gleichgrosse, fast hühnereidicke [illegible] (vergleiche Pat. Nr. 22 Tab. II und II b im Teil II), anschauliche Demonstration von konservativem Vorgehen (selbst bei sehr grosser Saktosalpinx Möglichkeit der Bewahrung vor [illegible] Sterilisierung in Form von einer bilat. Exstirpation).



Abb. 1. Intraoperatives Bild nach Öffnung der Bauchdecken (Pat. Nr. 47), bilat. fixierte, kranke T[illegible]bensack (vergleiche Abb. 9 und 10), rechtsseitig, verdickt und etwas eingeschnittener Exsudat im Douglas; salpingostomie bilat. + res. tub. et ov. amb. 5 1/2 Jahre vor jetziger Operation.



Abb. 2. Laparoskopie 7 Monate post op. (Pat. Nr. 42), keine Adhäsionen, frei bewegliche und offene T[illegible]benstümpfe, rechts Passage der ersten Tropfen der Methylenblaulösung (gleich darauf ebenfalls Passage links, vergleiche Abb. 11); beachte die feine T[illegible]benschleimhaut auf der rechten Seite.



Abb. 3. Intraoperatives Bild (Pat. Nr. 47). Beginn der Arbeit auf der anderen Seite m[illegible] der Auslösung des rechten T[illegible]bensackes (vergleiche Abb. 12) aus dem Ovarium; beachte die Operationstechnik: Präparation mit Hilfe von thermoelektrischer Nadelelektrode und Spülung anstelle der Operationsfeldreinigung mit Tupfern, keine Halteinstrumente direkt am Gewebe.



Abb. 4. Intraoperatives Bild (Pat. Nr. 47). Auslösung des [illegible] T[illegible]bensackes aus dem Ovarium abgeschlossen, beachte die durch die Tubenpräparation im Ovarium bei erhaltene Grube und die [illegible]r geringfügige Blutung der [illegible] gewechselten an den Wundkanten liegenden feuchten Bauchtücher (nach einer bisherigen Operationsd[illegible]er von etwa 3 1/2 Stunden!).



Abb 9 Präop Hysterosalpingogramm (Pat Nr 42) vor einigen Jahren in auswärtiger Klinik bilat. Salpingostomie mit Resektion von 3 5 beider Tuben bilat kurze Tubensäcke (vergleiche Abb.)



Abb Dieselbe Pat wie auf Abb 9, beachte die Drucksteigerung während der Kontrastfullung (hierdurch Vermeidung von falschen negativen Resultaten) Beide Bilder haben die gleiche Verkleinerung vom Original



Abb 9 Präop Hysterosalpingogramm (Pat Nr 4) or einigen Jahren in auswärtiger Klinik bilat. Salpingostomie mit Resektion von 3 5 beider Tuben bilat. kurze Tubensacke (vergleiche Abb)



Abb Dieselbe Pat wie auf Abb. 9, beachte die Drucksteigerung während der Kontrastfullung (hierdurch Vermeidung von falschen negativen Resultaten). Beide Bilder haben die gleiche Verkleinerung om Original



Abb. 11 Hysterosalpingogramm 8 Monate post op dieselbe Pat. wie auf Abb. 9 und 10 schnelle bilat. Passage durch nicht geweitete Tuben (vergleiche Abb 2) in freie Bauchhöhle



Abb. 12. Präop Hysterosalpingogramm (Pat. Nr 4) grosse und kräftig geweitete Tubensack bei grazilem Uterus (vergleich Abb 3 und 4)



Abb. 3 Hysterosalpingogramm 8 Monate post op., dieselbe Pat. wie auf Abb. schnelle bilat. Passage durch nicht geweitete Tuben in freie Bauchhöhle (vergleiche Abb. 5), derzeit gravidität m. VI.

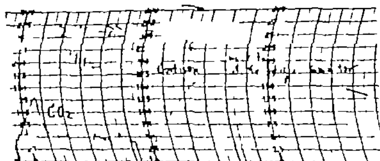


Abb. 4 Vortäuschung einer guten Passage (Pat. Nr. 39) durch die Insufflation allein (mit CO auf der Kurve bezeichnet). Aufdeckung des Abflusshindernisses erst durch die wegen unleidlicher Schmerzen der Patientin abgebrochene Hydropertubation (mit Cortison bezeichnet). Weitmannsinstrument (siehe auch Abb. 5)

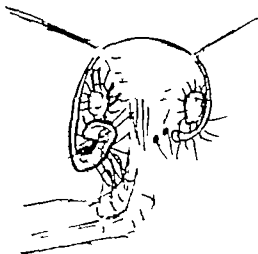


Abb 15 Dieselbe Pat. wie auf Abb 14 Skizze an Hand der präop Laparoskopie reichliche Adh = + + + eine geringe Menge der Farblösung ist in die perituberen Adh. lateral der li. Amp gepresst worden keine Fimbrien sichtbar

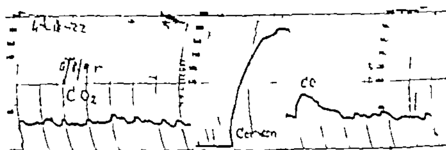


Abb 16 Dieselbe Pat ie auf Abb 14 und 5 post op. Hydropertubation Nr II 3 1/2 Wochen nach Op recht normale etwas flache Wellen 35–55 mm sehr schnelle schmerzf eie Passage 180 mm, Grafaxin trument (siehe auch Abb 7 und 17)

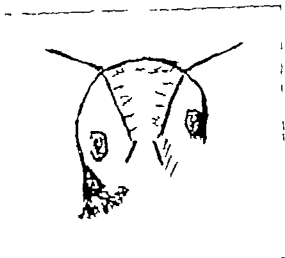


Abb. 7 Dieselbe Pat. wie auf Abb. 4–6. Skizze an Hand einer Laparoskopie 9 Monate post op., nur eine minimale Adh. = (+) zwischen re. Tube und re. Ovarium (Adh. um re. lig. sacrouterinum wurden nicht während Op. gelöst), normaler Fimbrientrichter B. (siehe Abb. 7) und kleiner re., bilat. sehr schnelle Passage.

Beseitigung. Die Hydropertubation ist zuverlässiger als eine einfache Insufflation, die leichter übersehbare Fehlerquellen in sich birgt (siehe z.B. Abb. 14). Bei ihrer Ausführung wird an unserer Klinik zuerst eine Kurve mit Hilfe der CO_2-Insufflation geschrieben, danach wird die Spülflüssigkeit (zur Zeit 40 ml physiol. NaCl-Lösung, 50 mg Hydrocortodrin® [Hydrocortisonacetat, AB Astra, Södertälje] und 200 000 I. E. gepuffertes Benzylpenicillin-Natrium [AB Novo, Kopenhagen] direkt in das CO_2-Schlauchsystem eingeschaltet, worauf die Flüssigkeit mit Hilfe des CO_2-Druckes des Insufflationsapparates in bzw. durch die Tuben gedrückt wird. Hierdurch wird eine objektive und korrekt registrierbare Kontrolle der Spülung ermöglicht (siehe z.B. Abb. 16) im Gegensatz zu dem subjektiven Daumendruck des einen Spritzenkolben betätigenden Arztes. Die Spülung wird mit einer nochmaligen Insufflation abgeschlossen. – Der Penicillinzusatz zur Flüssigkeit wurde als Infektionsprophylaxe nach Konsultierung von Kollegen des bakteriologischen Institutes und des Infektions-

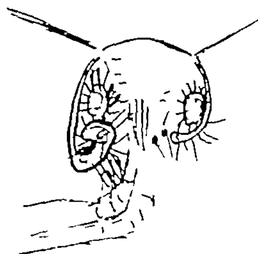


Abb 15 Dieselbe Pat. wie auf Abb 14 Skizze an Hand der präop Laparoskopie reichliche Adh = + + + eine geringe Menge der Farblösung ist in die peritubaren Adh. lateral der li. Amp gepresst worden, keine Fimbrien sichtbar

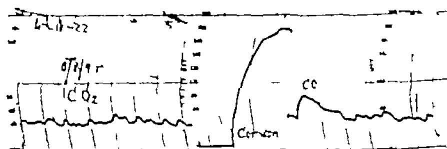


Abb 16 Dieselbe Pat. wi auf Abb 4 und 15 post op Hydropertubation Nr II 3 1/2 Wochen nach Op recht normale etwas flach Wellen, 35–55 mm sehr schnelle schmerzfreie Passage 180 mm Grafaxinstrument (siehe auch Abb 7 und 7)

Ursachen zusammenhängen, gute Resultate verhindern (Holden und Sovak, 1932 Gepfert, 1939 ten Berge und Tik Lok, 1954 Rock *et al* 1954 Vara, 1959 Green Armytage, 1960 Caplier 1964 Palmer 1966a Vara, 1967) Die zitierten Verfassergruppen sind nur ein Bruchteil der auf diesen Gebieten erschienenen Arbeiten. Beim Studium der Literatur über postoperative Verwachsungen (Literatur siehe Swolin 1966a, 1966b) wird einem klar dass das Operationstrauma und vor allem das Peritonealtrauma von ausschlaggebender Bedeutung sind Jackson (1958) behauptet sogar dass die Bildung von Verwachsungen direkt dem Trauma proportional ist.

Aufgrund der ebengenannten Fakta erscheint es dem Verfasser selbstverständlich, dass bei Fertilitätsoperationen jede Operationstechnik darauf ausgehen muss, das Operationstrauma so gering wie möglich zu gestalten und alle adhäsionsauslösenden Faktoren auf ein Minimum zu begrenzen Wie weit lassen sich heute auch innerhalb der Gynäkologie die im vorhergehenden beschriebenen Forderungen und Möglichkeiten zur Verminderung von postoperativen Adhäsionen in die Wirklichkeit umsetzen? Zur Beantwortung dieser Frage wurde deshalb versucht, bei den beschriebenen Fertilitätsoperationen folgende Technik und Gesichtspunkte zur Anwendung kommen zu lassen. So kleine und feine Instrumente wie möglich (siehe z.B Abb. 3 und 6) so feines Nahtmaterial wie möglich (z.B atraumatisches, langsam resorbierbares Catgut vom Typ 000 000 oder 00 000 – weniger heftige Resorptionsentzündung durch langsam resorbierbares Catgut –) behutsames (siehe z.B Abb 3, 4 und 8) und somit langsames Operieren (siehe Operationszeiten in Tab. II b im Teil II) scharfes Durchtrennen aller zu teilenden Gewebestrukturen und keine sogenannte stumpfe Lösung von Verwachsungen (Jackson 1958) Präparieren – abgesehen von sehr wenigen Ausnahmen – nur mit Hilfe thermo-elektrischer Nadelelektrode (siehe Abb. 3 und 6) um die Bildung von Verwachsungen einzuschränken (Kelterborn 1890 Küstner 1890 v Dembowski, 1891 ten Brink, 1898 Trowbridge 1929 Reichert *et al.* 1939) möglichst blutarmes Operieren (siehe z.B Abb. 3, 4 und 8) Operieren in einer Art feuchten Kammer (siehe z.B Abb. 3 4 und 8) die das Peritoneum vor Austrocknung bewahrt (Walt

krankenhauses gewählt (wegen der geringen Möglichkeit des Auftretens von eventuellen toxischen oder allergischen Nebenwirkungen) Die Möglichkeit einer eventuellen Begünstigung von Verwachsungen durch einen Penicillinzusatz zur Spülflüssigkeit ist erst in der letzten Zeit (Vara 1967) bekannt geworden und wird in nächster Zukunft Gegenstand näherer Nachforschungen werden – In den letzten Jahren hat der Verfasser mit sehr zufriedenstellendem Resultat fast ausschliesslich die bereits vorher erwähnte kleine Cervixvakuumglocke nach Malmström Thorén als Insufflations- und Spülkanüle verwendet. Seit 1964 steht unserer Klinik ein Grafaxinsufflationsinstrument Modell RTP mit thermo-elektrischem Schreiber zur Verfügung, vorher war ein Gynograph nach Weisman im Gebrauch Um später im Teil II eine Möglichkeit zu haben die Zeit der Passage einheitlich beschreiben zu können wurden folgende Bezeichnungen gewählt Sehr schnell (1) schnell (2) recht schnell (3–4) etwas langsam (5–6) langsam (7–10) sehr langsam (>10) Die Zahlen in den Klammern geben die Zeit (mit Hilfe der Zahl der Felder zwischen groben Strichen auf den Registrierungskurven) an in der der Druck maximal war – Hierbei ist zu berucksichtigen dass die Zeit von Strich zu Strich bei dem Grafaxinstrument mit der langsamen Einstellung I die wir immer benutzen 1 Minute ist während sie beim Weismaninstrument zwischen zwei groben Strichen nur 30 Sekunden ist die Angaben in den Tabellen II a und II b sind der besseren Verständlichkeit halber alle so angegeben (eventuell nach Umrechnung) als ob sie mit dem Grafaxinstrument gewonnen waren.

Operation und Operationstechnik

Versucht man näher zu ergründen warum eigentlich die Fertilitätsoperationen und insbesondere die Tubarplastiken so schlechte Resultate haben so ist ganz offenbar dass neben anderen Ursachen (wie z.B mangelhafte Voruntersuchung, fehlerhafte Technik ungeeignete Instrumente und geringe Erfahrung des Operateurs [Westman 1951 Greenhill 1956 Green Armytage, 1958 Palmer 1960 Chiara 1966 Hayashi 1966 Shirodkar 1966 Vara 1967]) vor allem die postoperativen Verwachsungen die natürlich teilweise mit den eben genannten

5. Tag nach Op	0,25 mg Decadron × 2
	1 Tetradectodrag × 4
6–10 Tag nach Op	0 25 mg Decadron × 2
	2 Sulfadontabl. × 2
11–20 Tag nach Op	2 Sulfadontabl. × 2

Die Naht des Peritoneum wird mit Catgut (fortlaufende Naht) ausgeführt, die Faszie wird mit einzelnen Knopfnähten versorgt (Catgut abwechselnd mit synthetischem Nahtmaterial) Die Schließung der Haut erfolgt mit etwa 3–4 Knopfnähten aus synthetischem Material und einzelnen Agraffen. Die Entfernung der Agraffen geschieht in der Regel zwischen dem 3.–6 Tag, die Entfernung der Hautnähte etwa am 8 oder 9 Tag Die Patientinnen werden einen Tag nach der ersten postoperativen Hydropertubation das heisst am 10. Tag post op entlassen (manchmal ist es aufgrund von Feiertagen oder ähnlichem auch schon der 9. oder erst der 11 Tag gewesen)

Das zu Anfang der Operationsserie geplante intraoperative Photographieren aller Fälle (siehe Abb 1 3 4 und 8) liess sich leider aufgrund von technischen und organisatorischen Schwierigkeiten nicht routinemäßig durchführen so dass bedauerlicherweise nur wenige gelungene Bilder von einigen wenigen Operationen zur Verfügung stehen.

Postoperative Untersuchung

Die von dem Verfasser angestrebte, rein routinemässige post operative Untersuchung aller Fertilitätsoperationen besteht aus 3 postoperativen Hydropertubationen einer Hysterosalpingographie und einer Photolaparoskopie (nähere Einzelheiten über diese Untersuchungen finden sich im Kapitel über die präoperativen Untersuchungen) Die postoperativen Laparoskopien (seit 1964 kommt das Photolaparoskop zur Anwendung) werden vom Verfasser ausgeführt, ebenso wie der überwiegende Teil aller Hydropertubationen

Die erste postoperative Hydropertubation geschieht am 9 Tag post op d.h. noch während des Klinikaufenthaltes. Die zweite

hard 1893) Anwendung von Lupenbrille und sogar Operationsmikroskop (Walz, 1959) bei schwierigem Präparieren und vor allem beim Arbeiten an den Tuben selbst und schliesslich die Benutzung von Mitteln die der Adhäsionsbildung entgegenwirken (nähere Literatur und Einzelheiten siehe Swolin 1966a 1966b, 1967a)

Die Operation wird vorzugsweise wenige Tage nach Abschluss einer Menstruation durchgeführt, um ein möglichst grosses Intervall zwischen Operation und nächster Menstruation zu haben.

Die Patientinnen unserer Klinik erhalten zur Zeit der Fertilitätsoperation zwecks Verminderung von Adhäsionen eine Glukokortikoidtherapie und im Zusammenhang damit eine Infektionsprophylaxe. Die Behandlung geschieht mit folgenden Präparaten Syntodecin® (Rolitetracyclinnitrat AB Astra Södertälje) Tetradecin Novum® (Tetracyclinhexametaphosphat, AB Astra Södertälje) Sulfadon® (N Sulfanilyl 4 isopropoxybenzamid und Sulfamerazin J R. Geigy A G Basel) Decadron (Dexamethason 21 Phosphat bzw Dexamethason Merck Sharp & Dohme International New York) und Hydrocortodrin® (Hydrocortisonacetat, AB Astra Södertälje)

Das Behandlungsschema für die Adhäsionsprophylaxe mit Glukokortikoiden ist zur Zeit folgendes

Tag vor Op	2 Tetradecindrag (à 0 25 g)×2
Abend vor Op	8 (evtl bis zu 24) mg Decadron i.m.
Operationsmorgen	24 mg Decadron i.m.
während Op	0 7 g Syntodecin i v
	2000 mg Hydrocortodrin intraperitoneal
Operationsabend	8 mg Decadron i.m
1 Tag nach Op	0 7 g Syntodecin i v
	8 mg Decadron i.m.×2
2 Tag nach Op	1 mg Decadron peroral×4
	1 Tetradecindrag ×4
3 Tag nach Op	0 5 mg Decadron×4
	1 Tetradecindrag ×4
4 Tag nach Op	0 5 mg Decadron×2
	1 Tetradecindrag ×4

Swolin, Kurt, Acta obst. et gynec. scandinav. 46, 231, 1967

Aus der Frauenklinik (Professor Sam Brody) der Universität in Göteborg, Schweden

50 FERTILITÄTSOPERATIONEN

Teil II. Material und Resultate

VON

KURT SWOLIN

Das Material des Verfassers besteht aus 50 Fertilitätsoperationen, zusammengefasst in den Operationsserien 1961 1963 1964 1965 und 1966 (im Jahre 1962 war der Verfasser zeitweise an anderer Klinik) In der Jahresgruppe 1961 finden sich 13 Patientinnen, die entsprechenden Zahlen für die anderen Gruppen sind 1963 10 Pat. 1964 8 Pat. 1965 17 Pat. und 2 Pat. aus dem Jahre 1966 die bereits eine Nachuntersuchung durchgemacht haben. Pat. Nr 11 und 48 sind ein und dieselbe Person Die Einteilung in Jahresgruppen wurde vorgenommen um das Material leichter verfolgen und bearbeiten zu können. Methodik und Technik der Operationen waren im Laufe der Jahre kleineren Veränderungen unterworfen worden siehe z.B die Änderung der intraperitonealen Glukokortikoidmenge in Tabelle II b Im Laufe der Jahre ist es wie deutlich aus den Tabellen II a und II b zu ersehen ist, mehr und mehr gelungen, komplette Vor und Nachuntersuchungen durchzuführen.

Die erste Operation der hier präsentierten Fälle war im Februar 961 und die letzte im Mai 1966. Da das Jahr 1962 praktisch weg fällt, ist es ein Material von knapp 5 Jahren Das Material ist unausgelesen und umfasst alle Fälle die vom Verfasser unter den Kauteien einer Fertilitätsoperation behandelt wurden es befinden sich nämlich im Material 3 Patientinnen deren primäre Operationsindikation nicht eine Sterilität war die aber auf besonderen Wunsch mit der speziellen, vom Verfasser bei Fertilitätsoperationen angewendeten Technik operiert wurden (Pat. Nr 24 26

(bzw dritte) postoperative Hydropertubation wird kurz vor dem Ovulationstermin der ersten (bzw zweiten) Menstruation nach der Operation durchgeführt. Die Abbildung 16 zeigt eine postoperative Hydropertubationskurve (siehe dazu auch Abb 7) In der im Teil II publizierten Tabelle II b ist mit Hydropertubation immer wenn nicht anders vermerkt die 3 postoperative Hydropertubation gemeint.

Zur Vereinfachung (für sowohl Patientin als auch Krankenhaus) versuchen wir die postoperative Hysterosalpingographie mit der Photolaparoskopie die wir einen Tag später ausführen zu kombinieren Es wird jetzt angestrebt, die Untersuchungen schon 6 Monate nach der Operation kurz vor einem geschätzten Ovulationstermin durchzuführen (falls keine Gravidität eingetreten ist) Die Abbildungen 11 und 13 zeigen postoperative Hysterosalpingogramme (vergleiche dazu die präoperativen Röntgenbilder auf den Abb 9 10 und 12) Während der Photolaparoskopie wird gleichzeitig die Passage mit Hilfe einer Farblösung geprüft. Laparoskopiebilder mit Passage der Blaulösung durch die geglückte Stomie einer operierten Saktosalpinx zeigen die Abbildungen 2 und 5

Das Literaturverzeichnis der im Teil I zitierten Verfasser befindet sich im Teil II

Passage während der Hysterosalpingographie z.B., schliesst also nicht eine Salpingostomie aus (siehe z.B. Pat. 33, 39 und 50 in Tab. IIa und IIb sowie Abb. 15 in Teil I). Werden nur Adhäsionen – wenn auch schwere – zwischen Ampulle und angrenzendem Gewebe gelöst und danach kein Eingriff mehr an der Tube selbst vorgenommen, so ist dies als eine Salpingolyse zu betrachten.

Das gesamte Material kann in folgende Operationstypen gruppiert werden

salpingostomia	33	(27 bilat., 6 unilat. an der einzigen Tube)
implantatio tubae	5	(2 bilat., unilat. an der einzigen Tube mit einer kontralateralen Salpingostomie)
salpingolysis		(4 bilat. 2 unilat. an der einzigen Tube 4 einseitige kombiniert mit kontralateralen Eingriffen)
enucl. myom. + coagul. foc. endometr.	2	
	50	

Bei der Klassifizierung der Operationen muss darauf geachtet werden – um später vergleichbare Operationsgruppen zu schaffen – dass, falls eine bilaterale Operation ausgeführt wurde, eine Patientin immer in der Gruppe registriert wird, in der der leichteste Eingriff ausgeführt wurde (siehe z.B. Pat. 11 in Tab. IIb). Das bedeutet mit anderen Worten, dass eine Patientin mit salpingostomia sin. + salpingolysis dx. in der Liste der Salpingolysen aufgeführt werden muss, da eine Salpingolyse der leichtere Eingriff oder, richtiger ausgedrückt, der Eingriff mit der grösseren Chance einer postoperativen Gravidität ist. – Der Verfasser nimmt hierbei an, dass die wohl allgemein akzeptierte Reihenfolge (im Hinblick auf die Zunahme der Graviditätschancen) folgende ist: Salpingostomia, implantatio tubae, salpingolysis. – Hierbei ist weiter zu beachten, dass die Angabe der intraoperativ gefundenen Adhäsionen ebenfalls eine gewisse Graduierung der operationstechnischen Schwierigkeiten zulässt, auch bei der Salpingolyse.

Neun Frauen hatten zur Zeit der Operation ein Alter von 35 Jahren oder mehr. Die älteste Patientin war 39 und die jüngste

29 30 und 31) Keine Patientin ist aufgrund der Schwere von Verwachsungen von einer Operation zurückgestellt worden. Es befinden sich also in dem präsentierten Material nicht wenige Patientinnen die sicherlich von vielen Operateuren aufgrund der Adhäsionen nicht einer Fertilitätsoperation unterworfen worden wären Die *langste Dauer der Sterilität war 15 Jahre die kürzeste* ein halbes Jahr Ende November 1966 wurden alle Patientinnen, von denen sich nicht irgendwelche Angaben aus den letzten Monaten in den der Klinik zur Verfügung stehenden Papieren fanden per Brief nach Graviditäten befragt. Die langste Beobachtungszeit nach der Operation ist also 5 Jahre und 10 Monate die kürzeste ein halbes Jahr

Die Tabelle II a enthält die Diagnose (mit der Dauer der Sterilität in der Klammer) die präoperativen Untersuchungen und *eventuelle Bemerkungen alles Fall für Fall fur alle 50 Operationen* Aus der Tabelle II b ersieht man das Alter und anamnestische Daten der Patientin den Typ und die Dauer der Operation (reine Operationszeit vom ersten Schnitt bis zur letzten Agraffe) die Menge der intraperitoneal applizierten Glukokortikoide, die Ausbreitung der intraabdominalen Adhasionen während und nach der Operation (zur Zeit der Laparoskopie) die postoperativen Nachuntersuchungen eventuelle Graviditäten (aufgeteilt in Aborte, Geburten und ektopische Graviditäten) und Bemerkungen. Aus *Gründen der Platzersparnis sind 2 derzeitige Schwangerschaften* in der Spalte Geburt mitaufgefuhrt worden Die Ausdehnung von Verwachsungen wird auf folgende Weise in der Tabelle angegeben 0=keine Verwachsungen (+)=eine minimale Verw +=leichte Verw ++=massige Verw +++=reichliche Verw (nähere Differenzierung bei S w o l i n 1967 a)

Alle Eingriffe waren kombinierte Operationen das heisst in keinem Fall wurde nur eine Salpingostomie Salpingolyse oder Tubarimplantation durchgefuhrt es waren z.B oft gleichzeitig Lösungen von Verwachsungen oder (und) Eingriffe an den Ovarien im Laufe der Operationen ausgeführt worden (siehe die Spalte Operation in Tab II b)

Als Salpingostomie fasst der Verfasser eine Operation auf bei der ein neues Stoma geschaffen wird, – mitunter stösst man auch in der Literatur auf den Ausdruck Neostomie – *Eine geringfügige*

[illegible]

Nr	Diagnose	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
1	[illegible]	[illegible]	[illegible]	—	—	—	—	—	—	—	—
2	[illegible]	[illegible]	—	—	—	—	—	[illegible]	—	—	—
3	[illegible]	[illegible]	—	[illegible]	—	—	—	[illegible]	[illegible]	—	—
	[illegible]	[illegible]	—	—	[illegible]	[illegible]	— [illegible]	[illegible]	[illegible]	[illegible]	—
	[illegible]	[illegible]	[illegible]	—	—	[illegible]	—	[illegible]	—	[illegible]	—
	[illegible]	[illegible]	[illegible]	—	[illegible]	[illegible]	—	[illegible]	[illegible]	[illegible]	[illegible]
	[illegible]	[illegible]		—	[illegible]	[illegible]	—	[illegible]	[illegible]	[illegible]	—
	[illegible]	—	[illegible]	—	—	—	—	[illegible]	—	[illegible]	—
	[illegible]	[illegible]	—	[illegible]	—	—	—	[illegible]	—	—	—
10	[illegible]	[illegible]	[illegible]	—	[illegible]	—	[illegible]	[illegible]	[illegible]	—	—
11	[illegible]	[illegible]	—	—	—	—	—	—	—	[illegible]	[illegible]
12	[illegible]	[illegible]	—	—	—	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	—
13	[illegible]	[illegible]	[illegible]	—	—	[illegible]	—	[illegible]	[illegible]	[illegible]	—
14	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	[illegible]	[illegible]	[illegible]	—	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	—

[illegible]

[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	+++ +++	—	[illegible]	[illegible]	[illegible]	—	—	—	[illegible]
[illegible]	[illegible]	++	[illegible]	—	[illegible]	[illegible]	[illegible]	—	—	—
[illegible]	[illegible]	++	[illegible]	[illegible]	[illegible]	[illegible]	—	[illegible]	—	[illegible]
[illegible]	[illegible]	+++	[illegible]	[illegible]	[illegible]	[illegible]	—	—	—	[illegible]
[illegible]	[illegible]		[illegible]	[illegible]	[illegible]	[illegible]	—	—	—	[illegible]
[illegible]	[illegible]		[illegible]	[illegible]	[illegible]	[illegible]	—	—	—	[illegible]
[illegible]	[illegible]		[illegible]	[illegible]		[illegible]	—	[illegible]	—	[illegible]
[illegible]	[illegible]	+—	[illegible]	[illegible]	[illegible]	[illegible]			—	[illegible]
[illegible]	[illegible]		[illegible]			[illegible]	—		—	[illegible]
[illegible]	[illegible]		[illegible]	[illegible]	[illegible]	[illegible]				[illegible]
[illegible]	[illegible]		[illegible]	[illegible]	[illegible]	[illegible]			—	[illegible]
[illegible]	[illegible]		[illegible]	[illegible]	[illegible]	[illegible]	—	[illegible]	—	—
[illegible]	[illegible]	++ ( )	[illegible]	[illegible]	[illegible]	[illegible]	—	—	—	—

[illegible]

[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
16	[illegible]	[illegible]	[illegible]	—	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	—	[illegible]
17	[illegible]	—	—	—	—	—	—	[illegible]	[illegible]	[illegible]		
	[illegible]	[illegible]	—	—	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	—	
19	[illegible]	[illegible]	[illegible]	—	[illegible]	[illegible]	—	[illegible]	[illegible]	[illegible]	[illegible]	
20	[illegible]	[illegible]	[illegible]	—	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	
	[illegible]	[illegible]	[illegible]	—	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
22	[illegible]	[illegible]	—	—	—	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
23	[illegible]	[illegible]	[illegible]	[illegible]	—	[illegible]	—	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
24	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
25	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	—	—
26	[illegible]	[illegible]	[illegible]	—	—	—	—	—	—			[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	—	[illegible]	—	—	[illegible]	[illegible]	[illegible]	[illegible]	
28	[illegible]	[illegible]	[illegible]	—	[illegible]	[illegible]	—	[illegible]	[illegible]	[illegible]	[illegible]	

[illegible]

Nr	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
29	[illegible]	[illegible]	[illegible]	—	—	—	—	[illegible]	—	—		[illegible]
30	[illegible]	—	[illegible]	—	—	—	—	—	—	—	—	[illegible]
31	[illegible]	[illegible]	—	—	—	—	—	—	—	—	—	[illegible]
32	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	—	[illegible]
33	[illegible]	[illegible]	[illegible]	—	—	—	—	—	—	—	—	—
34	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	—	[illegible]
35	[illegible]	[illegible]	[illegible]	—	—	[illegible]	—	[illegible]	—	[illegible]	—	[illegible]
36	[illegible]	[illegible]	[illegible]	[illegible] CO_2 [illegible]	—	—	[illegible]	[illegible]	[illegible]	[illegible]	—	[illegible]
37	[illegible]	[illegible]	[illegible]	—	—	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
38	[illegible]	[illegible]	[illegible]	—	—	—	[illegible]	[illegible]	[illegible]	[illegible]	—	[illegible]
39	[illegible]	[illegible]	[illegible]	[illegible]	—	—	[illegible]	[illegible]	[illegible]	[illegible]		[illegible]
40	[illegible]	[illegible]	[illegible]	—	—	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	—

[illegible]

[illegible]	[illegible]	[illegible]	[illegible]		[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	[illegible]	[illegible]	++		[illegible]	[illegible]	[illegible]	[illegible]	—	—	—	[illegible]
	[illegible]	[illegible]	++	++	[illegible]	[illegible]	[illegible]	[illegible]	—	—	[illegible]	[illegible]
	[illegible]	[illegible]	+++		[illegible]	[illegible]	[illegible]	[illegible]	—	—	—	[illegible]
	[illegible]	[illegible]	++		[illegible]	[illegible]		[illegible]	—	—	—	[illegible]
	[illegible]	[illegible]	++		[illegible]	[illegible]		[illegible]	—	[illegible]	—	[illegible]
	[illegible]	[illegible]	+++		[illegible]	[illegible]		[illegible]	[illegible]			[illegible]
	[illegible]	[illegible]	+++	—	—	[illegible]		[illegible]				[illegible]
	[illegible]	[illegible]	++	++	[illegible]	[illegible]	[illegible]	[illegible]			—	—
	[illegible]	[illegible]			[illegible]	[illegible]	[illegible]	[illegible]				—
	[illegible]	[illegible]			[illegible]	[illegible]	[illegible]	[illegible]	—	—	—	[illegible]
	[illegible]	[illegible]			[illegible]	[illegible]	[illegible]	[illegible]				[illegible]
	[illegible]	[illegible]			[illegible]	[illegible]		[illegible]			—	[illegible]

[illegible]

[illegible]

[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
29	[illegible]	[illegible]	[illegible]	—	—	—	—	[illegible]	—	—		[illegible]
30	[illegible]	—	[illegible]	—	—	—	—	—	—	—		[illegible]
31	[illegible]	[illegible]	—	—	—	—	—	—	—	—		[illegible]
32	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
33	[illegible]	[illegible]	[illegible]	—	—	—	—	—	—	—	—	
34	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	—	[illegible]
35	[illegible]	[illegible]	[illegible]	—	—	[illegible]	—	[illegible]	—	[illegible]	—	[illegible]
36	[illegible]	[illegible]	[illegible]	[illegible]	—	—	[illegible]	[illegible]	[illegible]	[illegible]		[illegible]
37	[illegible]	[illegible]	[illegible]	—		[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
38	[illegible]	[illegible]	[illegible]	—	—	—	[illegible]	[illegible]	[illegible]	[illegible]	—	[illegible]
39	[illegible]	[illegible]	[illegible]	[illegible]	—	—	[illegible]	[illegible]	[illegible]	[illegible]	—	[illegible]
40	[illegible]	[illegible]	[illegible]	—	—	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	

[illegible]

[illegible]	[illegible]	[illegible]	[illegible]		[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	[illegible]	[illegible]	+++	(+)	[illegible]	[illegible]	[illegible]	[illegible]	—	—	—	[illegible]
	[illegible]	[illegible]	++		[illegible]	[illegible]	[illegible]	[illegible]	—	—	—	[illegible]
	[illegible]	[illegible]	++	++	[illegible]	[illegible]	[illegible]	[illegible]	—	—	—	[illegible]
	[illegible]	[illegible]	++		[illegible]	[illegible]	[illegible]	[illegible]	—	—	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	+++	+++	[illegible]	[illegible]	[illegible]	[illegible]			—	[illegible]
[illegible]	[illegible]	[illegible]	++		[illegible]	[illegible]	[illegible]	[illegible]	—	—	—	[illegible]
[illegible]	[illegible]	[illegible]				[illegible]	[illegible]	[illegible]	—	[illegible]	—	[illegible]
[illegible]	[illegible]	[illegible]			[illegible]	[illegible]	[illegible]	[illegible]	—	—	—	[illegible]
[illegible]	[illegible]	[illegible]		++	[illegible]	[illegible]	[illegible]	[illegible]	—	—	—	[illegible]
	[illegible]	[illegible]			[illegible]	[illegible]	[illegible]	[illegible]	—	—	—	[illegible]

Tabelle [illegible] Diagnose und [illegible] Untersuchungen (Fortsetzung)

Nr	Diagnose	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
41	[illegible]	[illegible] Passage	[illegible] Passage [illegible]	—	—	path.	biphasisch	normal	sehr gut	[illegible]	—	[illegible]
42	[illegible]	[illegible]	[illegible] Passage [illegible]	—	neg	path.	biphasisch	normal	gut	[illegible]	—	[illegible]
43	[illegible]	Passage [illegible]	[illegible] Passage	[illegible] Passage, 2?0 mm	—	—	biphasisch	[illegible]	[illegible]	[illegible]	—	[illegible]
44	[illegible]	[illegible] Passage	[illegible]	—	neg	path.	biphasisch	normal	gut	[illegible]	neg	
45	[illegible]	[illegible] Passage [illegible]	[illegible] Passage [illegible]	[illegible]	neg	path.	biphasisch, [illegible]	normal	[illegible]	[illegible]	—	
46	[illegible]	[illegible] Passage	[illegible]	—	—	—	biphasisch	normal	[illegible]	[illegible]	—	[illegible]
47	[illegible]	[illegible] Passage [illegible]	[illegible]	—	neg	path.	biphasisch	normal	sehr gut	[illegible]	neg	—
48	[illegible]	[illegible] Passage	[illegible] Passage	[illegible] Passage, [illegible] mm	—	path.	biphasisch	normal [illegible]	sehr gut	[illegible]	neg	[illegible]
	[illegible]	[illegible] Passage [illegible]	[illegible] Passage	[illegible] mm	neg	path.	biphasisch	normal	[illegible]	[illegible]	—	[illegible]
50	[illegible]	[illegible]	[illegible] Passage [illegible]	[illegible]	—	—	biphasisch	[illegible]	—	—	—	[illegible]

[illegible]

Die Hysterosalpingographie und auch die Laparoskopie geben Resultate von Spätkontrollen. Die Hydropertubations- oder Insufflationsresultate dagegen nehmen eine Zwischenstellung zwischen Früh- und Spätkontrollen ein da meistens die dritte post operative Spülung oder Durchblasung (etwa 6–10 Wochen post op) in der Tabelle II b angegeben wird. Abgesehen von einem Fall mit einer unilateralen Implantation – bei dem aber eine post operative Hysterosalpingographie und Laparoskopie durchgeführt wurden – sind alle Operationen mit Hydropertubation (evtl. Insufflation) nachkontrolliert worden in den meisten Fällen dreimal. Bei 2 Patientinnen fand sich keine Passage (die eine Pat. [Nr 8] mit nur einer Hydropertubation 9 Tage post op hatte später 2 Lebendgeburten, bei der anderen [Nr 16] war die erste postoperative Spülung [19 Tage post op] noch normal gewesen) Die Passagerate ist also 95,9 %

Die postoperativen Verwachsungen können nur bei den Patientinnen die mit einer Laparoskopie (evtl Relaparotomie) nachkontrolliert werden beurteilt werden. In 28 Fällen (von 36) trat gemäss der Tabelle II b eine Verminderung des Ausmasses der Verwachsungen ein – Hierzu ist zu bemerken dass in 3 weiteren Fällen (Pat. Nr 16 19 und 36) die aufgrund der gewählten Art in der Tabelle II b Verwachsungen zu bezeichnen, mit + + + angegeben wurden, jedoch ebenfalls eine deutliche Verminderung von postoperativen Adhäsionen eingetreten war –

Im gesamten Material finden sich 18 Graviditäten das ist eine Graviditätsrate von 36 % Eine Patientin (Nr 1) ist nicht befragt worden und eine andere (Nr 2) hat nicht auf die Anfrage geantwortet beide sind also als negative Resultate zu werten (im Hinblick auf eine Gravidität) Die Graviditäten lassen sich wie folgt aufteilen

14 intrauterine Graviditäten	28,0 %	
Lebendgeburten		22,0 %
2 derzeitige Graviditäten		4,0 %
Abort		2,0 %
4 ektopische Graviditäten	8,0 %	
18 Graviditäten	36,0 %	
1 [illegible]		

18 Jahre alt. Das Durchschnittsalter in dem präsentierten Operationsmaterial ist 28 7 Jahre

Die durchschnittliche Operationszeit von allen 50 Operationen ist 3 Stunden 36 Minuten Die längste Zeit war 5 Stunden und 10 Minuten die kürzeste 1 Stunde und 50 Minuten.

In dem gesamten Material finden sich 24 Fälle mit primärer und 21 Falle mit sekundärer Sterilität, die übrigen Fälle wurden auf grund von anderen Indikationen operiert, davon 3 akut (Pat. Nr 26 30 und 31)

Resultate

Eine komplette Spätkontrolle der Eingriffe im Hinblick auf Passage und Aussehen des Operationsfeldes wurde in 35 Fällen ausgeführt. In 39 von den 50 Operationsfällen konnte eine postoperative Hysterosalpingographie durchgeführt werden Hierbei liess sich 36mal eine Passage (freie oder nicht freie uni oder bilaterale) nachweisen das ist eine Passagerate von 92 3 %

Eine Laparoskopie (bzw Photolaparoskopie) kontrollierte bei 36 Operationen das Endresultat. Bei 2 der mit dem Laparoskop nachkontrollierten Fälle konnte wegen Verdacht auf intrauterine Gravidität oder wegen Instrumentfehlers keine Prüfung der Passage vorgenommen werden beide Patientinnen hatten doch später eine Lebendgeburt so dass man mit Fug und Recht in diesen Fällen eine sichere Passage annehmen darf Bei den übrigen 34 laparoskopischen Nachkontrollen fand sich eine Passage (freie oder nicht freie uni- oder bilaterale) in 31 Fallen das ist eine Passagerate von 91,2 %

In 7 Fällen wo keine oder nur eine teilweise Spätkontrolle möglich war ist es zu einer (oder zwei) Lebendgeburt gekommen in einem Teil dieser Fälle war der Eintritt einer Gravidität vor der Nachkontrolle der Anlass keine Nachuntersuchung durchzuführen In einem 8 Fall (Pat. Nr 13) kam es vor der postoperativen Laparoskopie zu einer ektopischen Gravidität. In einigen Fällen war eine Nachkontrolle aus verschiedenen mehr oder weniger persönlichen Gründen aufgeschoben worden (4 Patientinnen waren an einen anderen Ort verzogen) Nur 2 Patientinnen haben direkt eine Nachkontrolle abgelehnt.

30 und 31) waren aus anderen Indikationen operiert worden.

Von den 33 Salpingostomiefällen wurden 28 röntgenologisch nachkontrolliert = 84 % (3 verzogen, 1 schwere Salp. vor Kontrolle und 1 Ablehnung der Kontrolle). Bei 27 Frauen ergab die Hysterosalpingographie eine Passage (freie oder nicht ganz freie, uni- oder bilaterale), das ist eine Passagerate von 96,4 %. Eine freie Passage auf mindestens einer Seite fand sich bei 20 Patientinnen.

26 von 33 Patientinnen mit Salpingostomie unterzogen sich einer postoperativen Laparoskopie = 78,8 % (3 verzogen, 1 normale Grav. und 1 ektop. Grav. vor Kontrolle, 1 schwere Salp. vor Kontrolle und 1 Ablehnung der Kontrolle). Bei 2 Frauen (Nr. 18 und 27) konnte die Passage während der Laparoskopie nicht kontrolliert werden. Von den übrigen 24 Patientinnen hatten 23 eine Passage der instillierten Farblösung, das ist eine Passagerate von 95,8 %. In 21 Fällen ließ sich mindestens auf einer Seite eine gute und schnelle Passage nachweisen.

Die Passagerate bei der Hydropertubation (bzw. Insufflation) war 97 %.

Bei den 33 Salpingostomiepatientinnen fanden sich total 12 Graviditäten = 36,4 %, die wie folgt aufgeteilt werden können.

8 intrauterine Graviditäten	24,2 %	
6 Lebendgeburten		18,2
derzeitige Graviditäten		6,1
4 ektopische Graviditäten	12,1 %	
12 Graviditäten	36,3 %	

Nimmt man nicht die Totalanzahl der Graviditäten, sondern rechnet Patientinnen mit Gravidität, so kommt man auf 9 Patientinnen = 27,3 % mit einer Gravidität (oder mehr). Folgende Unterteilung läßt sich machen:

6 Pat. mit intrauteriner Gravidität	18,2 %	
5 Pat. mit Lebendgeburt		15,2 %
Pat. mit derzeitiger Gravidität		3,0 %
3 Pat. mit ektopischer Gravidität	9,1	
9 Patientinnen	27,3 %	

Abgesehen von Allergien, z.B. gegen Penicillin (bei Hysterosalpingographien und Hydropertubationen), sehr vereinzelten (nach [illegible]

Berechnet man die Resultate per Patientin mit Gravidität, so ergeben sich andere Zahlen da einige Patientinnen zweimal schwanger wurden Hierdurch ergeben sich natürlich schlechtere aber dafür mehr exakte die wirklichen Verhältnisse zeigende Ziffern mit nur 14 Patientinnen die eine Gravidität (oder mehr) hatten = 28 % Die weitere Aufteilung ist:

11 Pat. mit intrauteriner Gravidität	22,0 %	
9 Pat. mit Lebendgeburt		18,0 %
1 Pat. mit derzeitiger Gravidität		2,0 %
1 Pat. mit Abort		2,0 %
3 Pat. mit ektopischer Gravidität	6,0 %	
14 Patientinnen	28,0 %	

Wendet man die zuletzt aufgeführte Berechnungsart an so hatten die 24 primärsterilen Frauen 6 Graviditäten (4 Lebendgeburten 1 derzeitige Grav m VI und 1 ektopische Grav) und die 21 sekundärsterilen Frauen 7 Graviditäten (5 Lebendgeburten, 1 Abort m. III und 1 ektopische Grav) Eine Patientin (Nr 30) die aufgrund einer ektopischen Gravidität akut operiert wurde hatte später noch 2 ektopische Graviditäten

Für die Beurteilung der Resultate von Fertilitätsoperationen ist es sehr wichtig die Resultate per Operationstyp aufzuteilen da sonst leicht Missverständnisse aufkommen weil in den publizierten Arbeiten die schlechten Resultate der schweren Operationen durch die guten Ergebnisse der leichten Eingriffe verschleiert werden Im Hinblick hierauf sind die Salpingostomien von besonderem Interesse da sie – richtig ausgeführt – schwierige und zeitraubende Eingriffe sind meist die schlechtesten Resultate haben und oft nur einen Bruchteil des publizierten Operationsmaterials ausmachen so dass nur wenige Arbeiten mit einer grösseren Anzahl Salpingostomien veröffentlicht worden sind. Aus diesen Gründen und weil sie den grössten Teil der Fertilitätsoperationen des Verfassers ausmachen sollen die Salpingostomieresultate dieser Arbeit für sich gesondert betrachtet werden

In dem Material des Verfassers finden sich 33 reine (wenn auch durch andere Eingriffe noch komplizierte) Salpingostomien, 27 bilaterale und 6 unilaterale (an einer einzigen Tube) 13 Frauen waren primär steril 16 sekundär steril und 4 (Nr .6 29

in der frühen Sekretionsphase geringer ist (siehe z.B. 10. und 18. Tag bei Pat. Nr. 4 in Tab. II b). Die Gefahr der Ausschwemmung eines befruchteten Eies ist jedoch nicht von der Hand zu weisen, weshalb für die Hydropertubation (und natürlich auch die Hysterosalpingographie) die Tage kurz vor der Ovulation vorgezogen werden. Die Deutung der Hydropertubationskurven ist nicht immer einfach, da mitunter eine langsame Passage bei niedrigem Druck (siehe z.B. Pat. Nr. 23 und 50) gegenüber einer schnellen Passage bei hohem Druck (in der Mehrzahl der Fälle) geschieht. – Ein höherer Druck bei der Passage scheint sich öfter bei dem Grafaxinstrument als bei dem Weismaninstrument zu finden. Eine Erklärung hierfür ist vielleicht, dass es bei dem Grafaxinstrument nicht so leicht ist, das CO_2-Volumen per Minute zu kontrollieren, bei dem Weismaninstrument hingegen lässt sich eine Menge von 50 ml/min leicht einstellen. – Auch wenn die Hydropertubation eine wertvolle und aufschlussreiche Untersuchungsmethode ist, so ist es doch die bestimmte Auffassung des Verfassers, dass sie nur im Zusammenhang mit Laparoskopie und Hysterosalpingographie richtig gedeutet werden kann.

Die Basaltemperaturkurve ist für die Erkennung einer Corpus-Luteum-Insuffizienz sicherlich von erheblicher Bedeutung, da zur Zeit für die Aufdeckung solcher Zustände und damit Behandlung sonst unerklärlicher Sterilitäten (siehe z.B. Pat. Nr. 18 in Tab. II b) noch keine anderen Methoden für den klinischen Gebrauch zur Verfügung stehen. – Die Beurteilung des Aussehens der Ovarialoberfläche kann vielleicht hier in Zukunft bei grösserer Erfahrung des Operateurs auch einige Fingerzeige geben. – Im übrigen ist der Verfasser der Meinung, dass auch eine narbengeschädigte oder mit etwas Bindegewebe überzogene Oberfläche des Eierstockes der Grund einer postoperativen Sterilität sein kann, wenn eine gute Passage der Tuben (anatomisch und funktionell) nachgewiesen worden ist. Auch die chemische Untersuchung des Ejakulats und ein besseres Verständnis des Postcoitaltestes dürften in Zukunft dazu beitragen, in gewissen Fällen mit „guter Passage" den Schlüssel für eine unerklärliche Sterilität zu finden. Wünschenswert wäre es vor allem, bessere und mehr physiologische (= deszendierende?) Untersuchungsmethoden der Funktion der Eileiter für die praktische Anwendung in der Klinik

bei anderen Operationen vorkommenden) Catgutfisteln im subcutanen Fettgewebe und einer suspekten Salpingitis nach Hydropertubation ohne Penicillin fand sich eigentlich nur eine Komplikation die der in *dieser Arbeit angewendeten speziellen Methodik* und insbesondere der Anwendung von sehr grossen Dosen von Glukokortikoiden zur Last gelegt werden kann Eine Patientin (Nr 40) klagte in den ersten Wochen post op uber eine deutliche Gewichtszunahme und ein geschwollenes Gesicht das allgemeine Wohlbefinden war jedoch nicht gestört und die Erscheinungen verschwanden ohne jegliche Therapie

Diskussion

In dem Material des Verfassers sind 5 Patientinnen deren primäre Operationsindikation nicht eine Sterilität war Bei 3 Patientinnen findet sich jedoch eine Sterilität mit in der Diagnose die beiden anderen Frauen (Nr 26 und 29) *waren sich aber trotz der* anderen vorherrschenden Symptome ihrer Sterilitat bewusst und baten deshalb dass man während der Operation auch die Sterilität behandeln möge Aufgrund dieser Umstände wurden die Patientinnen in das Material der Fertilitätsoperationen miteinbegriffen

Die prä- und postoperativen Untersuchungen haben gezeigt dass Hysterosalpingographie und Laparoskopie mitunter verschiedenartige Resultate ergeben Auf dieses Verhalten wird in einer späteren Arbeit (Swolin und Rosencrantz) näher eingegangen werden Weiter ist es seit längerer Zeit der Wunsch des Verfassers um der röntgenologischen Untersuchung der Eileiter noch mehr Aussagekraft und Objektivität zu geben die Hysterosalpingographie immer mit Hilfe eines Insufflationsinstrumentes nach Art einer Hydropertubation ausführen zu lassen

Noch mehr in die Augen fallend ist mitunter der Unterschied zwischen Hydropertubation (bzw Insuffl.) auf der einen Seite und der röntgenologischen und vor allem laparoskopischen Untersuchung auf *der anderen Seite* (siehe z.B Pat. Nr 20 und 48) Der Zeitpunkt einer Hydropertubation ist etwas problematisch. In Übereinstimmung mit den von Lindahl und Helander (1960) für die Hysterosalpingographie gefundenen Resultaten glaubt der Verfasser dass der Tonus im medialen Teil der Tube

in der frühen Sekretionsphase geringer ist (siehe z.B 10 und 18 Tag bei Pat. Nr 4 in Tab II b) Die Gefahr der Ausschwemmung eines befruchteten Eies ist jedoch nicht von der Hand zu weisen weshalb für die Hydropertubation (und natürlich auch die Hysterosalpingographie) die Tage kurz vor der Ovulation vorgezogen werden. Die Deutung der Hydropertubationskurven ist nicht immer einfach, da mitunter eine langsame Passage bei niedrigem Druck (siehe z.B Pat. Nr 23 und 50) gegenüber einer schnellen Passage bei hohem Druck (in der Mehrzahl der Fälle) geschieht. – Ein höherer Druck bei der Passage scheint sich öfter bei dem Grafaxinstrument als bei dem Weismaninstrument zu finden Eine Erklärung hierfür ist vielleicht, dass es bei dem Grafaxinstrument nicht so leicht ist, das CO_2-Volumen per Minute zu kontrollieren bei dem Weismaninstrument hingegen lässt sich eine Menge von 50 ml/min leicht einstellen. – Auch wenn die Hydropertubation eine wertvolle und aufschlussreiche Untersuchungsmethode ist, so ist es doch die bestimmte Auffassung des Verfassers, dass sie nur im Zusammenhang mit Laparoskopie und Hysterosalpingographie richtig gedeutet werden kann.

Die Basaltemperaturkurve ist für die Erkennung einer Corpus-Luteum-Insuffizienz sicherlich von erheblicher Bedeutung, da zur Zeit für die Aufdeckung solcher Zustände und damit Behandlung sonst unerklärlicher Sterilitäten (siehe z.B Pat. Nr 18 in Tab II b) noch keine anderen Methoden für den klinischen Gebrauch zur Verfügung stehen – Die Beurteilung des Aussehens der Ovarialoberfläche kann vielleicht hier in Zukunft bei grösserer Erfahrung des Operateurs auch einige Fingerzeige geben. – Im übrigen ist der Verfasser der Meinung, dass auch eine narbengeschädigte oder mit etwas Bindegewebe überzogene Oberfläche des Eierstockes der Grund einer postoperativen Sterilität sein kann, wenn eine gute Passage der Tuben (anatomisch und funktionell) nachgewiesen worden ist. Auch die chemische Untersuchung des Ejakulats und ein besseres Verständnis des Postcoitaltestes dürften in Zukunft dazu beitragen in gewissen Fällen mit „guter Passage" den Schlüssel für eine unerklärliche Sterilität zu finden. Wünschenswert wäre es vor allem, bessere und mehr physiologische (= deszendierende?) Untersuchungsmethoden der Funktion der Eileiter für die praktische Anwendung in der Klinik

bei anderen Operationen vorkommenden) Catgutfisteln im subcutanen Fettgewebe und einer suspekten Salpingitis nach Hydropertubation ohne Penicillin fand sich eigentlich nur eine Komplikation die der in dieser Arbeit angewendeten speziellen Methodik und insbesondere der Anwendung von sehr grossen Dosen von Glukokortikoiden zur Last gelegt werden kann. Eine Patientin (Nr 40) klagte in den ersten Wochen post op über eine deutliche Gewichtszunahme und ein geschwollenes Gesicht das allgemeine Wohlbefinden war jedoch nicht gestört und die Erscheinungen verschwanden ohne jegliche Therapie

Diskussion

In dem Material des Verfassers sind 5 Patientinnen deren primäre Operationsindikation nicht eine Sterilität war Bei 3 Patientinnen findet sich jedoch eine Sterilität mit in der Diagnose die beiden anderen Frauen (Nr 26 und 29) waren sich aber trotz der anderen vorherrschenden Symptome ihrer Sterilitat bewusst und baten deshalb dass man während der Operation auch die Sterilität behandeln möge Aufgrund dieser Umstände wurden die Patientinnen in das Material der Fertilitatsoperationen miteinbegriffen

Die prä und postoperativen Untersuchungen haben gezeigt dass Hysterosalpingographie und Laparoskopie mitunter verschiedenartige Resultate ergeben Auf dieses Verhalten wird in einer späteren Arbeit (Swolin und Rosencrantz) näher eingegangen werden Weiter ist es seit längerer Zeit der Wunsch des Verfassers um der röntgenologischen Untersuchung der Eileiter noch mehr Aussagekraft und Objektivitat zu geben die Hysterosalpingographie immer mit Hilfe eines Insufflationsinstrumentes nach Art einer Hydropertubation ausführen zu lassen

Noch mehr in die Augen fallend ist mitunter der Unterschied zwischen Hydropertubation (bzw Insuffl) auf der einen Seite und der röntgenologischen und vor allem laparoskopischen Untersuchung auf der anderen Seite (siehe z.B Pat. Nr 20 und 48) Der Zeitpunkt einer Hydropertubation ist etwas problematisch. In Übereinstimmung mit den von Lindahl und Helander (1960) für die Hysterosalpingographie gefundenen Resultaten glaubt der Verfasser dass der Tonus im medialen Teil der Tube

in der frühen Sekretionsphase geringer ist (siehe z.B 10 und 18 Tag bei Pat. Nr 4 in Tab. II b) Die Gefahr der Ausschwemmung eines befruchteten Eies ist jedoch nicht von der Hand zu weisen, weshalb für die Hydropertubation (und natürlich auch die Hysterosalpingographie) die Tage kurz vor der Ovulation vorgezogen werden. Die Deutung der Hydropertubationskurven ist nicht immer einfach, da mitunter eine langsame Passage bei niedrigem Druck (siehe z.B Pat. Nr 23 und 50) gegenüber einer schnellen Passage bei hohem Druck (in der Mehrzahl der Fälle) geschieht. – Ein höherer Druck bei der Passage scheint sich öfter bei dem Grafaxinstrument als bei dem Weismaninstrument zu finden. Eine Erklärung hierfür ist vielleicht, dass es bei dem Grafaxinstrument nicht so leicht ist, das CO_2-Volumen per Minute zu kontrollieren bei dem Weismaninstrument hingegen lässt sich eine Menge von 50 ml/min leicht einstellen – Auch wenn die Hydropertubation eine wertvolle und aufschlussreiche Untersuchungsmethode ist, so ist es doch die bestimmte Auffassung des Verfassers dass sie nur im Zusammenhang mit Laparoskopie und Hysterosalpingographie richtig gedeutet werden kann.

Die Basaltemperaturkurve ist für die Erkennung einer Corpus-Luteum-Insuffizienz sicherlich von erheblicher Bedeutung, da zur Zeit für die Aufdeckung solcher Zustände und damit Behandlung sonst unerklärlicher Sterilitäten (siehe z.B Pat. Nr 18 in Tab II b) noch keine anderen Methoden für den klinischen Gebrauch zur Verfügung stehen. – Die Beurteilung des Aussehens der Ovarialoberfläche kann vielleicht hier in Zukunft bei grösserer Erfahrung des Operateurs auch einige Fingerzeige geben. – Im übrigen ist der Verfasser der Meinung, dass auch eine narbengeschädigte oder mit etwas Bindegewebe überzogene Oberfläche des Eierstockes der Grund einer postoperativen Sterilität sein kann, wenn eine gute Passage der Tuben (anatomisch und funktionell) nachgewiesen worden ist. Auch die chemische Untersuchung des Ejakulats und ein besseres Verständnis des Postcoitaltestes dürften in Zukunft dazu beitragen, in gewissen Fällen mit „guter Passage" den Schlüssel für eine unerklärliche Sterilität zu finden. Wünschenswert wäre es vor allem, bessere und mehr physiologische (=deszendierende?) Untersuchungsmethoden der Funktion der Eileiter für die praktische Anwendung in der Klinik

bei anderen Operationen vorkommenden) Catgutfisteln im subcutanen Fettgewebe und einer suspekten Salpingitis nach Hydropertubation ohne *Penicillin fand sich eigentlich nur eine Komplikation* die der in dieser Arbeit angewendeten speziellen Methodik und insbesondere der Anwendung von sehr grossen Dosen von Glukokortikoiden zur Last gelegt werden kann *Eine Patientin* (Nr 40) klagte in den ersten Wochen post op über eine deutliche Gewichtszunahme und ein geschwollenes Gesicht das allgemeine Wohlbefinden war jedoch nicht gestört und die Erscheinungen verschwanden ohne jegliche Therapie

Diskussion

In dem Material des Verfassers sind 5 Patientinnen deren primäre Operationsindikation nicht eine Sterilität war Bei 3 Patientinnen findet sich jedoch eine Sterilität mit in der Diagnose die beiden anderen Frauen (Nr 26 und 29) waren sich aber trotz der anderen vorherrschenden Symptome ihrer Sterilität bewusst und baten deshalb dass man während der Operation auch die Sterilität behandeln möge. Aufgrund dieser Umstände wurden die Patientinnen in das Material der Fertilitätsoperationen miteinbegriffen

Die prä und postoperativen Untersuchungen haben gezeigt dass Hysterosalpingographie und Laparoskopie mitunter verschiedenartige Resultate ergeben Auf dieses Verhalten wird in einer späteren Arbeit (*Swolin und Rosencrantz*) *näher eingegangen* werden Weiter ist es seit längerer Zeit der Wunsch des Verfassers um der röntgenologischen Untersuchung der Eileiter noch mehr Aussagekraft und Objektivität zu geben die Hysterosalpingographie immer mit Hilfe eines Insufflationsinstrumentes nach Art einer Hydropertubation ausführen zu lassen

Noch mehr in die Augen fallend ist mitunter der Unterschied zwischen Hydropertubation (bzw Insuffl) auf der einen Seite und der röntgenologischen und vor allem laparoskopischen Untersuchung auf der anderen Seite (siehe z.B Pat. Nr 20 und 48) Der Zeitpunkt einer Hydropertubation ist etwas problematisch. In Übereinstimmung mit den von Lindahl und Helander (1960) für die Hysterosalpingographie gefundenen Resultaten glaubt der Verfasser dass der *Tonus im medialen Teil der Tube*

nisse bei der Passageprüfung in dieser Arbeit erlauben vielleicht den Schluss, dass die vom Verfasser – aufgrund von vorher erwähnten theoretischen Erwägungen und zitierten Erfahrungen – angestrebte Operationstechnik (siehe Abb 3, 4 und 8) nicht ganz ohne Einfluss auf die Resultate gewesen sein mag. Die Zahl der Patientinnen in dem eigenen Material, die bereits früher einer (Fertilitäts-) Operation unterzogen wurden ist noch klein sie spricht jedoch recht eindeutig für die angestrebte Technik (siehe z.B Pat. Nr 18 37 38 39 und 41) Auch die eigene Erfahrung im Fall 23, bei der aufgrund eines vermuteten malignen Colontumors auf die konventionelle Operationstechnik übergegangen wurde zeigt in die gleiche Richtung.

Aus wissenschaftlichen Gründen und um schneller ein grösseres Material sammeln zu können hat der Verfasser in der präsentierten Arbeit keinen Abstand von Patientinnen mit reichlichen Verwachsungen (35 Fälle) genommen es ist daher wahrscheinlich mit einer Überrepräsentation von Fällen mit reichlichen Verwachsungen – also Gruppe III, gemäss Hayashi (1966) – gegenüber anderen publizierten Arbeiten zu rechnen. Die Resultate sind jedoch nicht so enttäuschend, dass es nach Ansicht des Verfassers berechtigt ist, in Zukunft das Ausmass der Verwachsungen für die Ablehnung von Fertilitätsoperationen verantwortlich zu machen. Die Auswahl sollte von anderen Faktoren wie z.B. Ovarialfunktion Aspermie, Inkompatibilität gegenüber dem Ejakulat etc. abhängig gemacht werden.

Anhand des eigenen Materials lassen sich, abgesehen von den operationstechnischen Versagern folgende mögliche Ursachen für das Nichteintreten einer erwünschten intrauterinen Schwangerschaft herausstellen An die erste Stelle möchte der Verfasser eine mit den bisher zur Verfügung stehenden Mitteln nicht aufzudeckende, aber theoretisch zu fordernde Dysfunktion der Eileiter stellen. Die relativ hohe Zahl der ektopischen Graviditäten die leider auch als reine Versager zu betrachten sind, weist in diese Richtung. Weitere Möglichkeiten sind in Kürze Nicht ganz einwandfreie Postcoitalteste (16 Fälle) Verdacht auf Ovarialdysfunktion (15 Fälle) Endometriose (10 Fälle) Salpingitis isthmica nodosa (6 histol. verifizierte oder klinisch suspekte Fälle) Salpingitis (post nicht propter op) Spasmus der Tube (mit Hydro-

zur Verfügung zu haben (abgesehen von der Anwendung von z.B radioaktivem Gold oder gefärbten Stärkekörnern)

Für die Untersuchung des Einflusses von vorhergehenden Operationen und Graviditäten (normalen und nicht normalen) sowie von Befunden bei Hysterosalpingographien Laparoskopien oder Hydropertubationen (im Hinblick auf die Tube selbst) als auch weiter von Endometriose Salpingitis isthmica nodosa (verifizierter oder klinisch verdächtiger) Basaltemperatur oder Postcoitaltest auf das Zustandekommen von normalen oder ektopischen Graviditäten ist das vorliegende Material noch zu klein. Es ergeben sich jedoch bereits interessante Fragestellungen (siehe z.B Pat. Nr 3 6 18 27 44 und 47) Der Verfasser hofft, nach Sammlung eines grösseren Materials die Relationen dieser einzelnen Faktoren zueinander näher untersuchen zu können

Der Fall der Pat Nr 22 zeigt dass man mit einer äusserst konservativen Einstellung (vergleiche auch z.B Abb 8 im Teil I) sogar bei der Behandlung von sehr grossen Tubensäcken (die vielleicht im allgemeinen immer den Tubenräubern [Sellheim] zum Opfer fallen) gute Resultate in Form von 2 postoperativen Lebendgeburten erhalten kann

Die in der Arbeit nachgewiesene Verminderung der Adhäsionen ist nach Ansicht des Verfassers das Verdienst sowohl der speziellen Operationstechnik als auch der durchgeführten Glukokortikoidtherapie – Durch Anwendung verbesserter anderer oder einer Kombination von mehreren Methoden wird es in Zukunft wahrscheinlich gelingen noch bessere Resultate im Hinblick auf die postoperativen Verwachsungen zu erzielen –

In 4 Fällen hat der Verfasser sich einer Lipid-Glukokortikoidkombination zur Adhäsionsprophylaxe bedient (siehe auch Swolin 1966b) Aufgrund der geringen Anzahl soll noch keine nähere Stellungnahme hierzu genommen werden. Das cushingoide Aussehen der einen Patientin mit sehr hohen Glukokortikoidmengen mahnt jedoch zum Nachdenken

Stellt man nun die Frage nach den Ursachen des Misslingens von Fertilitätsoperationen so muss man in erster Linie die rein operationstechnischen Versager von den technisch geglückten Eingriffen trennen Die Prüfung der Passage ergibt Anhaltspunkte für die anatomischen Ergebnisse der Operation Die guten Ergeb-

nisse bei der Passageprüfung in dieser Arbeit erlauben vielleicht den Schluss, dass die vom Verfasser – aufgrund von vorher erwähnten theoretischen Erwägungen und zitierten Erfahrungen – angestrebte Operationstechnik (siehe Abb 3, 4 und 8) nicht ganz ohne Einfluss auf die Resultate gewesen sein mag Die Zahl der Patientinnen in dem eigenen Material, die bereits früher einer (Fertilitäts-) Operation unterzogen wurden ist noch klein, sie spricht jedoch recht eindeutig für die angestrebte Technik (siehe z.B. Pat. Nr 18 37 38 39 und 42) Auch die eigene Erfahrung im Fall 23, bei der aufgrund eines vermuteten malignen Colontumors auf die konventionelle Operationstechnik übergegangen wurde zeigt in die gleiche Richtung

Aus wissenschaftlichen Gründen und um schneller ein grösseres Material sammeln zu können hat der Verfasser in der präsentierten Arbeit keinen Abstand von Patientinnen mit reichlichen Verwachsungen (35 Fälle) genommen es ist daher wahrscheinlich mit einer Überrepräsentation von Fällen mit reichlichen Verwachsungen – also Gruppe III, gemäss Hayashi (1966) – gegenüber anderen publizierten Arbeiten zu rechnen. Die Resultate sind jedoch nicht so enttäuschend, dass es nach Ansicht des Verfassers berechtigt ist, in Zukunft das Ausmass der Verwachsungen für die Ablehnung von Fertilitätsoperationen verantwortlich zu machen. Die Auswahl sollte von anderen Faktoren, wie z.B. Ovarialfunktion, Aspermie Inkompatibilität gegenüber dem Ejakulat etc., abhängig gemacht werden.

Anhand des eigenen Materials lassen sich, abgesehen von den operationstechnischen Versagern folgende mögliche Ursachen für das Nichteintreten einer erwünschten intrauterinen Schwangerschaft herausstellen. An die erste Stelle möchte der Verfasser eine mit den bisher zur Verfügung stehenden Mitteln nicht aufzudeckende aber theoretisch zu fordernde Dysfunktion der Eileiter stellen. Die relativ hohe Zahl der ektopischen Graviditäten die leider auch als reine Versager zu betrachten sind, weist in diese Richtung. Weitere Möglichkeiten sind in Kürze Nicht ganz einwandfreie Postcoitalteste (16 Fälle) Verdacht auf Ovarialdysfunktion (15 Fälle) Endometriose (10 Fälle) Salpingitis isthmica nodosa (6 histol. verifizierte oder klinisch suspekte Fälle) Salpingitis (post nicht propter op.) Spasmus der Tube (mit Hydro-

pertubation konstatiert) Auflösung der Ehe Ablehnung von *Nachkontrolle oder Nachbehandlung* sehr suspekte Tubentuberkulose Neurasthenie zusammen mit Oligopareunie kongenitale Genitaldysplasie (siehe Pat Nr 14) *eine eventuell mögliche Dominanz* des kontralateralen Ovarium – z.B bei einer einzelnen Tube (siehe Pat. Nr 43) – und die Abkapslung der Ovarialoberfläche durch Narbengewebe bei im übrigen guter Funktion der Tube (Die oben angegebenen Ziffern sind Minimiziffern da nicht alle Patientinnen komplett untersucht worden sind. Die Diagnosen umfassen sowohl histologische wie klinische Verdachts-Diagnosen In vielen Fällen besteht eine Kombination mehrerer möglicher Sterilitätsgründe.)

Bei der Berechnung der Passage wurden die Prozentzahlen auf die mit der jeweiligen *Untersuchungsmethode kontrollierten* Patientinnen berechnet die Ziffern im *Hinblick* auf Graviditäten wurden jedoch in Übereinstimmung mit Siegler (1964) auf die *Gesamtzahl der Operationen bezogen* Das sieht wie eine gewisse Inkonsequenz aus die sich jedoch durch Rucksichtnahme auf internationale Interessen (Vergleichbarkeit der Resultate) erklären lässt. – Man kann nicht verlangen dass Kollegen in anderen Ländern die nicht die Vorteile eines allgemeinen Gesundheitsdienstes haben die Passage aller Patientinnen mit Hysterosalpingographie und Laparoskopie nachkontrollieren können die Zahlen der Passage sollten daher auf die wirklich kontrollierten Patientinnen bezogen werden –

Zusammenfassung

Nach einem kurzen Einblick in die Literatur der Operationsresultate werden 50 Fertilitätsoperationen mit den dazu ausgeführten Vor und Nachuntersuchungen ausführlich beschrieben in der Hoffnung hiermit exakte und eingehend auszuwertende Grundlagen zu schaffen für eine Zusammenarbeit von Fertilitätsoperateuren über die Grenzen der eigenen Klinik hinaus Die Operationstechnik wird im einzelnen begrundet und näher beschrieben es wird der Versuch gemacht eine Art von möglichst atraumatischer und weitgehend *blutungsfreier Mikrotechnik* durchzuführen

Für das Gesamtmaterial war die Passagerate der Spätkontrolle mit der Hysterosalpingographie 92 % und mit der Laparoskopie 91 %. Die Kontrolle mit Hilfe der Hydropertubation bzw. Insufflation (im allgemeinen etwa 6–10 Wochen post op.) ergab eine Passage in 96 %. Die entsprechenden Ergebnisse für die im Material enthaltenen Salpingostomien waren 96 % bei der Hysterosalpingographie, 96 % bei der Laparoskopie und 97 % bei der Hydropertubation bzw. Insufflation.

Im gesamten Material fanden sich total 36 % Graviditäten, die weiter aufgeteilt wurden in 28 % intrauterine Graviditäten (22 % Lebendgeburten, 4 % derzeitige Grav. sowie 2 % Aborte) und 8 % ektopische Graviditäten. Bei Berechnung der Resultate per Patientin mit Gravidität ergaben sich folgende Zahlen: 28 % Patientinnen mit Gravidität, 22 % mit intrauteriner Gravidität (18 % Lebendgeburten, 2 % derzeitige Grav. sowie 2 % Aborte) und 6 % Patientinnen mit ektopischer Gravidität.

Für die 33 Salpingostomien (27 bilat. und 6 unilat. an der einzigen Tube) waren die Totalresultate folgende: 36 % Graviditäten, 24 % intrauterine Graviditäten (18 % Lebendgeburten sowie 6 % derzeitige Grav.) und 12 % ektopische Graviditäten. Bei Angabe der Resultate per Patientin mit Gravidität fanden sich folgende Zahlen: 27 % Patientinnen mit Gravidität, 18 % Patientinnen mit intrauteriner Gravidität (15 % Lebendgeburten und 3 % mit derzeitiger Grav.) und 9 % Patientinnen mit ektopischer Gravidität.

Eine Adhäsionsprophylaxe wurde mit sehr hohen Dosen von Glukokortikoiden versucht.

Meinem Chef Professor Sven Brody danke ich für die stete und liebenswürdige Hilfsbereitschaft sowie das wärmende Interesse bei der Durchführung dieser Arbeit. Professor Ulf Borell, meinem früheren Chef, bin ich zu tiefem Dank verbunden für die Hilfe und das freundliche Entgegenkommen, die den Beginn dieser Untersuchungen ermöglichten. Meinen Kollegen und dem Personal der Klinik möchte ich für alle Geduld und Hilfe, die mir die Durchführung dieser Arbeit erleichterten, meinen aufrichtigen Dank aussprechen. Dozent Ingmar Wickbom danke ich für die freundliche Zurverfügungstellung von Röntgenbildern der Röntgenabteilung II. Ich möchte nicht versäumen, an dieser Stelle Ausdruck zu geben für die Dankbarkeit, die ich gegenüber meinen Lehrern auf dem Gebiete der Fertilitätsoperationen empfinde, namentlich dem verstorbenen Professor Green-Armytage sowie Doktor Raoul Palmer und Professor Paavo Vara.

SUMMARY

A brief survey of the literature concerning the results of fertility operations is tabulated. The author describes in detail the results of the pre-operative and post-operative examinations made in conjunction with the 50 consecutive fertility operations which he performed between 1961 and 1966 with a quite uniform technique. The extensive presentation has been made in order to stimulate the detailed and precise description of techniques and results to permit future comparison between different centers.

The elaboration of the surgical technique employed is completely described. The goal was a type of microsurgery as atraumatic and bloodless as possible.

Passage of contrast medium was observed in 36 or 92 % of the 39 patients examined by hysterosalpingography. At laparoscopy (since 1964 photolaparoscopy) only 34 patients could be tested for passage which was positive in 31 or 91 % of these. The follow up hydropertubation (in 2 cases insufflation) showed passage in 96 % of 49 patients. Patency figures for the 33 salpingostomy patients were 96 % of 28 at hysterosalpingography, 96 % of 24 at laparoscopy and 97 % of 33 at hydropertubation (or 1 insufflation).

The incidence of post-operative pregnancy in the total material was 36 % which can be classified as 28 % intra uterine pregnancies (terminated by live birth 22 %, abortion 2 % and pregnant at the time of writing 4 %) and 8 % ectopic pregnancies. Analysis in regard to number of pregnant patients rather than total pregnancies provides the following information which is more relevant in regard to the recovery of tubal function: 28 % pregnant patients of which 22 % had intra-uterine pregnancies (terminated by live birth 18 %, abortion 2 % or pregnant at the time of writing 2 %) and 6 % patients with ectopic pregnancies.

Of the 33 patients treated with salpingostomy (27 bilaterally and 6 unilaterally on the one existing tube) the pregnancy figures were as follows: 36 % pregnancies, 24 % intra uterine pregnancies (live birth 18 %, pregnant at the time of writing 6 %) and 12 % ectopic pregnancies. The figures in regard to number of pregnant patients are 9 or 27 % pregnant, 6 or 18 % intra-uterine (5 or

15% terminated by live birth, and 1 or 3% pregnant at the time of writing) and 3 or 9% ectopic pregnancies.

Very large doses of glucocorticoids intended to diminish the formation of post-operative adhesions were administered. Favourable results of this therapy were noted in 31 or 86% of the 36 patients controlled by laparoscopy or reoperation (1 pat.)

LITERATURVERZEICHNIS

The American Society for the Study of Sterility Evaluation of the Barren Marriage, Birmingham/Alabama, Wiederdruck 962
Athanasiu G., Geburtsh. u. Frauenheilk 1 42 1944
ten Berge B. und *Tik Lok* T Ned. T Geneesk., 98 3659, 954
Bergman P Svenska Läk.-Tidn., 60 2 77 963
Bohm, E. und *Engfund*, S Acta obstet. gynec. scand., 26 329 946
ten Brink, F Z. Geburtsh. Gynäk., 38 276, 1898
Bruster E., Trompa de Falopio y Esterilidad de Causa Tubaria, Buenos Aires, 951
Caplier P pers. Mitteilung, 964
Chalier A. Gynéc. prat., 7 129, 956
Chiara A., pers. Mitteilung, 1966
Contamine A. Fertil. and Steril., 5, 334 1954
Dembowski Th. Cbl. Gynäk., 15 28 1891
Eguchi S Jap. J Fertil. u. Steril., 4 49 959, zit. Greenhill 960 961
Fertil and Steril. (Current Reviews) 1 4 2, 959
Gepfert J R., Amer J Obstet. Gynec., 38 298 1939
Grant A. und *Mackay* R., N Z. med. J 54 307 1955
zit. Greenhill, 962 963
Green-Armytage V zit. Solomons, 936
pers. Mitteilung, 958
J. Obstet. Gynaec. Brit. Emp 66 32, 959
Proc. Royal Soc. Med., 53 360 960
Greenhill J Amer J. Obstet. Gynec 33, 30, 937
Amer J Obstet. Gynec., 72 516 956
Year Book Obstet. Gynec 341 960 96
Year Book Obstet. Gynec., 360 962, 963
Gromadzki W Pam. XIV zjazdu PTG Krynica, 1960 zit. Nowosad, 962
Hanton E *Pratt* J und *Banner* E., Amer J. Obstet. Gynec., 89, 934, 1964
Hayashi M Referatband, 3. Weltkongr Gynäk. Obstet., Wien, 961
pers. Mitteilung, 966
Holden F und *Sovak*, F Amer J Obstet. Gynec., 24 684, 932
Holtz, F Compte intern. jubilaire Soc. franç. Gynéc., Paris 195
Jackson B. Surgery 44, 507 958

SUMMARY

A brief survey of the literature concerning the results of fertility operations is tabulated. The author describes in detail the results of the pre-operative and post-operative examinations made in conjunction with the 50 consecutive fertility operations which he performed between 1961 and 1966 with a quite uniform technique The extensive presentation has been made in order to stimulate the detailed and precise description of techniques and results to permit future comparison between different centers.

The elaboration of the surgical technique employed is completely described The goal was a type of microsurgery as atraumatic and bloodless as possible.

Passage of contrast medium was observed in 36 or 92 % of the 39 patients examined by hysterosalpingography At laparoscopy (since 1964 photolaparoscopy) only 34 patients could be tested for passage which was positive in 31 or 91 % of these. The follow up hydropertubation (in 2 cases insufflation) showed passage in 96 % of 49 patients Patency figures for the 33 salpingostomy patients were 96 % of 28 at hysterosalpingography 96 % of 24 at laparoscopy and 97 % of 33 at hydropertubation (or 1 insufflation)

The incidence of post operative pregnancy in the total material was 36 % which can be classified as 28 % intra-uterine pregnancies (terminated by live birth 22 % abortion 2 % and pregnant at the time of writing 4 %) and 8 % ectopic pregnancies. Analysis in regard to number of pregnant patients rather than total pregnancies provides the following information which is more relevant in regard to the recovery of tubal function 28 % pregnant patients of which 22 % had intra uterine pregnancies (terminated by live birth 18 % abortion 2 % or pregnant at the time of writing 2 %) and 6 % patients with ectopic pregnancies

Of the 33 patients treated with salpingostomy (27 bilaterally and 6 unilaterally on the one existing tube) the pregnancy figures were as follows 36 % pregnancies 24 % intra uterine pregnancies (live birth 18 % pregnant at the time of writing 6 %) and 12 % ectopic pregnancies. The figures in regard to number of pregnant patients are 9 or 27 % pregnant 6 or 18 % intra uterine (5 or

Swolin K. und *Rosencrantz M.*, In Vorbereitung
Trabe V. pers. Mitteilung, 966
Trowbridge E., New Engl. J. Med., *201* 1183 929
Vara P. Gynaecologia, *147* 445 959
– Ann. Chir. Gynaec. Fenn., *54* 225, 965
pers. Mitteilung, 967
Walthard, M., Corresp.-Bl. Schweiz. Aerzte 23, 513, 893
Walz W. Z. Geburtsh. u. Gynäk., 153, 49 959
Westman A., Acta obstet. gynec. scand., 30 86 951

Am 9. März 967 erhalten

Jedberg, H Acta obstet. gynec. scand., 31 Suppl. 1 1950
Kelterborn G Cbl. Gynäk 14 913 1890
Küstner H Arch. Gynäk., 161 135 1936
Küstner O., Cbl. Gynäk., 14 425 1890
Laliam N 5 Weltkongr Fertil. Steril., Stockholm 1966
Leblanc E. Diss. Paris unpubl., zit. Fertil and Steril. 1959
Lindahl J und *Helander C.-G* Gynaecologia (Basel) 150 205 1960
Mackey R., 5. Weltkongr Fertil. Steril., Stockholm 1966
Malmnäs C. Opuscula Medica 3 67 1958
Martin A. Handbuch der Krankheiten der weiblichen Adnexorgane Leipzig 1895
Martius H., Zbl. Gynäk., 73 547 1951
Mayer A., Beitr zur Fertil. und Steril., Beilageheft Z. Geburtsh., Bd. 151 Vol. 2 S 59 1959
Murray E Ann. Ostet. Ginec. 78 118 1956
Nowosad K. Reszczyński A. und *Weinbrenner L.* Gynaecologia, 153, 321 1962
Özaras H., pers. Mitteilung, 1967
Palmer R. und *Proust G* Bull. Féd. Soc. Gynéc. Obstét. Paris 5 548 1953
Palmer R. pers Mitteilung, 1960
– pers. Mitteilung, 1966 a
– 5 Weltkongr Fertil. Steril., Stockholm 1966 b
Pobedinski M Ann. Ostet. Ginec., 78 193 1956
Poradovský K. Cs. Gynek., 24 700 1959
Pous Puigmacia L. Rev esp Obstet. Ginec., T 19 213 und 299 1960
Reichert F Gerbrode F und *Halford F* Ann. Surg 110 669 1939
Rio F Tropea P und *Monti M* Riv Ostet. Ginec. 19 649 1964
Rock J., *Mulligan W* und *Easterday C.* Obstet. and Gynec 3 21 1954
Rust W Z Geburtsh. Gynäk. 160 79 1963
Sager Ph. Ugeskr Læg., 126 1191 1964
Sellheim H zit. Mayer 1959
Serdiucov zit. Pobedinski, 1956
Shirodkar V Contributions to Obstetrics and Gynaecology Edinburgh und London 1960
– West. J Surg. Obstet. Gynec. 69 253 1961
– pers. Mitteilung, 1966
Siegler A. und *Hellman L.* Fert. Steril., 7 170 1956
– Amer J Obstet. Gynec., 86 448 1963
Siegler A. Int. J Fertil., 9 561 1964
Solomons B J Obstet. Gynaec. Brit. Emp 43, 6 9 1936
Stenberg, H., pers. Mitteilung 1960
Swolin K. Acta obstet. gynec. scand. 45 451 1966 a
– Acta obstet. gynec. scand., 45 473 1966 b
– Acta obstet. gynec. scand., 46 204 1967 a
– Acta obstet gynec. scand. 46 19 1967 b

Swolin K. und Rosencrantz M., in Vorbereitung
Traka, V. pers. Mitteilung, 1966
Trowbridge E., New Engl. J. Med. 201, 1, 83, 1929
Vara P. Gynaecologia, 147, 445, 1959
Ann. Chir. Gynaec. Fenn., 54, 225, 1965
pers. Mitteilung, 1967
Walthard, M., Corresp.-Bl. Schweiz. Aerzte, 23, 5 3, 1893
Walz W. Z. Geburtsh. u. Gynäk., 153, 49, 1959
Westman, A. Acta obstet. gynec. scand. 30, 186, 1951

Am 9. März 1967 erhalten

Hallgrimsson, Jón Th. Acta obst. et gynec. scandinav. 46, 268, 1967
From the Department of Obstetrics and Gynaecology (A. Rydén M.D.) and the Department of Pathology (G. Björkman), Centrallasarettet, Borås, Sweden

CARCINOMA IN SITU OF THE ENDOCERVIX CORPUS UTERI AND BOTH OVIDUCTS

BY

JÓN TH. HALLGRIMSSON[1]

The progress in cytological diagnosis particularly after the pioneer work of *Papanicolou* and *Traut* (1941) has greatly stimulated interest in carcinoma in situ first described by *Rubin* (1910)

A special and rather rare type of carcinoma in situ is found, not only in the endocervix but also in the uterine cavity. This type has been described by *Fridell* (1958) who reported two cases and another one has been described by *Kairys et al.* (1964). We have had the opportunity to observe a similar case

Case History

The patient was a 54 year old para II menarche when 14 and menopause at the age of 51. She complained of a *foul-smelling, slightly yellowish discharge* and bilateral lower abdominal pain. Earlier she had been in good health, with no family history of tuberculosis, diabetes or malignant disease. Nor had she, after the menopause, experienced any abnormal bleeding. When first examined, she appeared to be in good health, with no signs of pulmonary or cardiac disease and a blood pressure of 150/90. Abdominal palpation revealed neither tenderness nor palpable masses. The temperature was 38.3 C.

On gynaecological examination, the vagina and vulva were normal, as was the uterus. Behind and to the right of the uterus there was a rounded rather hard mass, about the size of an egg, which was fixed but not attached to the pelvic wall. Sigmoidoscopy (20 cm) showed nothing abnormal. The erythrocyte sedimentation rate was 80 mm, haemoglobin 65 %, and a leuco-

[1] Present address: The Dept. of Obst. and Gyn., Landspitalinn, Reykjavik, Iceland



Fig. 1

cyte count 22,700 cu.mm. Se K was 3.8 mEq/l, Na 135 mEq/l and Cl 104 mEq/l. Serum protein was 7.4 and creatinin 2.1. There was slight anisocytosis and poikilocytosis. Tests for gonorrhea and syphilis were negative. Uterine curettage was performed and, with the aid of colposcope four biopsies were taken from the cervix.

Histological examination of the curettings showed an abundance of squamous epithelium, with considerable atypia, and all four biopsies from the cervix revealed carcinoma in situ. Four days after admission, the pelvic mass had enlarged so puncture, (colpotomi) was done. This yielded about 100 cc of yellowish, foul-smelling pus but on culture no bacterial growth could be demonstrated.

After the puncture, the pelvic mass almost disappeared, the patient became afebrile and was discharged from hospital. On readmission a month later she was symptom free and no pelvic mass was found, so laparotomy was performed followed by total hysterectomy with bilateral salpingo-oophorectomy plus appendicectomy (the appendix was normal). The findings were a small tubo-ovarian abscess ca 3×4 cm, on the right side and thick and indurated oviduct. The oviduct on the left side revealed signs of an old, healed salpingitis, without any abscess formation. Postoperative recovery was uneventful and the patient was discharged on the ninth day. Microscopic examination of the vaginal cuff and the portio vaginalis showed a little thickened, but regular and basally well demarcated squamous epithelium, normally differentiated towards the surface and without any signs of atypia.



Fig. 2

Sections from different segments of the endocervix and all sections from the uterine cavity (Fig. 1) showed an unevenly thickened atypical squamous surface epithelium, with poor differentiation and numerous mitotic figures. The atypical squamous epithelium was also found to have involved glandular structures as well some of them of considerable depth. Signs of invasive growth were not found. Sections from the thickened oviducts showed a considerable cell infiltration and fibrosis Even in the oviducts (Fig 2) the same type of squamous epithelium, as in the uterine corpus and endocervix was found Within the tubal lumina there was an abundance of atypical cells. No signs of invasive growth were found.

The atypical squamous epithelium found in the uterus and oviducts fullfilled the criteria for carcinoma *in situ*. One year postoperatively the patient was in good health, and no signs of malignancy were detected.

Discussion

The reports on carcinoma *in situ* of the uterine cavity are few and the author has found none with such an extension as the one here reported

Fridell (1958) has described two cases with such changes in the uterine cavity The first case was a 56 years old multipara, who

complained of a brownish vaginal discharge. A salpingo-oophorectomy had been done 6 years earlier On inspection a cervical tumour was detected. Hysterectomy was performed and carcinoma in situ found, both in the uterine cavity and endocervix.

The other case a 55 years old woman, sought advice because of a bloody discharge two years after the menopause. Cytological investigation showed malignant cells in material taken from the vagina and cervix. Microscopic investigation after hysterectomy showed that the endocervix and the endometrium were covered by non-invasive squamous epithelium. In this case, signs of invasive growth were also found in the endocervix.

Both these patients were without signs of metastases three years later Kairys et al. (1964) described one case of carcinoma in situ in the endometrium in a 57 years old coloured woman, who 3 1/2 years earlier had received X ray therapy because of a cervical cancer and who now was symptomfree At follow up cervical atresia and fibromyomata were found necessitating laparotomy

Most of the endometrium in this case showed changes compatible with carcinoma in situ. There were no signs of direct spread from the earlier detected carcinoma of the cervix.

Kistner (1964) related, as incidental findings three cases of carcinoma in situ of the oviducts, during a five year period. The four cases discussed, do not of course allow any general conclusions but they do show certain similarities. Thus their ages at the time of diagnosis show only a four year span and the average is well above that for carcinoma in situ of the cervix.

Reviewing the material in our district, during 1962 and 1963 the average age of the patients with carcinoma in situ of the cervix proved to be 38.9 years, which corresponds to the findings of most other investigators. The average age of the cases here discussed was thus 6–8 years more than that for invasive carcinoma of the cervix which in turn is about 10 years above the average age for non invasive carcinoma.

In all four cases, inflammatory changes were found, in our case a tubo-ovarian abscess in two cases discharge and in one—pyometra Thus raises the possibility of infection as an aetiological factor In the case reported by Kairys the patient had previously

received radiotherapy whether this is true for the other two cases is not known.

It is to be expected, that in the future, similar cases will be detected especially because of the already well known success of mass-screening in search of carcinoma of the cervix. As the average age of the patients discussed in this paper is well over fifty years it is desirable that future plans for cytological screening should include also patients in this age-group.

SUMMARY

A case of carcinoma in situ of the endocervix extending to the uterine cavity and oviducts is reported and certain similarities with earlier cases reported are discussed.

REFERENCES

Fridell G H Obst. & Gynec. *12*, 179 1958
Kairys L R. Dougherty C. M. Mickal A. Am. J Obst. & Gynec. *88*, 548, 1964
Kistner R. W Gynecology Principles and Practice Year Book Medical Publishers, 1964
Papanicolou G N and *Traut H F* Am. J Obst. & Gynec. *43* 1931 1941
Rubin I C Am. Journ. of Obst. *62* 668, 1910

Received on July 6th, 1966

Nilsson, Inga Marie and Kullander Stig, Acta obst. et gynec. scandinav. 46: 273, 1967

From the Coagulation Laboratory (Prof Inga Marie Nilsson) and the Department of Obstetrics and Gynecology (Prof Stig Kullander) Malmö General Hospital, University of Lund, Malmö Sweden

COAGULATION AND FIBRINOLYTIC STUDIES DURING PREGNANCY[1]

BY

INGA MARIE NILSSON AND STIG KULLANDER

It is now widely accepted that the activity of various coagulation factors increases as pregnancy advances. The fibrinolytic activity has been reported to be reduced in pregnancy but little is known about the behaviour of the individual components of the fibrinolytic system during pregnancy. Owing to the changes observed in coagulation activity during pregnancy the condition has been described as a "hypercoagulable state" (*Erichson* 1965). But no unanimity has been reached concerning the clinical significance of this hypercoagulability in pregnancy.

The purpose of the present investigation, in which determinations were made of the platelet adhesiveness and the components of the coagulation and fibrinolytic systems during different stages of pregnancy, was to obtain reference data for the evaluation of the clinical significance of alterations in the coagulation of the blood during the use of anovulatory drugs (*Nilsson* and *Kullander* 1967).

Methods

Collection of blood and assays of coagulation factors and fibrinolytic components. The blood was collected with the silicone technique and citrated plasma and serum were prepared as

[1] This investigation was supported by grants from the Swedish Medical Research Council.

19 - 5 - 462

described previously (*Nilsson Blombäck* and *v Francken*, 1957 *Paraskevas et al* 1962) The following determinations were made platelet count coagulation time, one-stage prothrombin time recalcification time of plasma prothrombin consumption platelet adhesiveness in citrated whole blood, AHF (f VIII) haemophilia B-factor (f IX) factor V prothrombin, factor VII and factor X (Owren s P&P-test) thrombin time and fibrinogen. Methods described previously were used for the determinations (*Nilsson Blombäck* and *Ramgren* 1961 *Nilsson* and *Olow* 1962 b *Nilèhn* and *Nilsson* 1964 *Cronberg, Nilsson* and *Silwer* 1966)

Fibrinolytic activity was assayed by determination of the activity of plasma and resuspended euglobulin precipitate on unheated fibrin plates (*Nilsson* and *Olow*, 1962 a) Plasminogen was determined by a clot method (*Nilsson Skanse* and *Gydell* 1957) Inhibitors of plasminogen activation by urokinase were measured according to *Paraskevas et al* (1962) The antiplasmin activity of serum was determined according to *Nilsson et al.* (1961) The inhibiting effect of serum on tissue activator from pig heart (antiactivator assay) was determined as described by *Nilsson Björkman v Studnitz* and *Hallén* (1961)

Clinical Material

Twenty-seven women were investigated during uncomplicated pregnancy In 15 of these women blood samples were drawn in the first and/or second and/or third trimester and/or 2–5 months after delivery (Table I) In the remaining 12 women blood samples were drawn immediately before 1/2–3 hrs after delivery and then on each of the first 4 days *post partum*

Results

The results of the coagulation and fibrinolytic studies during pregnancy are given in Table I The coagulation time platelet count, prothrombin consumption and platelet adhesiveness remained unchanged throughout pregnancy The values for P&P and fibrinogen gradually increased with the duration of preg-

nancy The AHF (f VIII) increased substantially already in the second trimester and in the last trimester it was invariably at least twice the initial value No significant change occurred in the levels of factor V haemophilia B-factor (f IX) or the thrombin time.

The fibrinolytic activity decreased and in the third trimester was practically nil. The plasminogen activity increased from a mean value of 113 per cent in the first trimester to 150 per cent in the third trimester The inhibitors of plasminogen activation by urokinase remained unchanged in all the patients except one in whom the level in the third trimester was 268 per cent of normal. We had no opportunity to check this value. The antiplasmin and antiactivator activities showed a moderate increase.

The results of the analyses performed 2–5 months after delivery were normal.

In 12 patients coagulation and fibrinolytic assays were performed immediately before and after delivery and during the first 4 *post partum* days (Table II)

The increased level of fibrinogen remained unchanged during these 4 days, but the AHF P&P and plasminogen decreased by about 20–30 per cent. Immediately before and after delivery only little or no spontaneous fibrinolytic activity could be demonstrated, but on the second day after delivery normal fibrinolytic activity reappeared. The antiactivator activity decreased gradually after delivery

Discussion

The plasma fibrinogen and factors VII and X are known to be increased in pregnancy (*Ratnoff* *Colopy* and *Pritchard* 1954 *Fresh* *Adams* and *Morgan* 1959 *Gillman* *Naldoo* and *Hathorn* 1959 *Talbert* and *Langdell* 1964 *Kasper* et al 1964 *Todd* 1965 *Loeliger* and *Koller* 1952 *Larrieu* *Soulier* and *Minkowski* 1952 *Alexander* et al 1956 *Fresh* *Ferguson* and *Lewis* 1956 *Pechet* and *Alexander* 1961 *Rutherford* et al 1964) Factor II or prothrombin has been shown to be only slightly affected (*Ratnoff* et al 1954 *Pechet* and *Alexander* 1961 *Kasper* et al.

Table I. *Coagulation and Fibrinolytic Studies in Pregnancy*

Mean Values and Ranges in Normal Pregnant Women	First trimester No of subjects 15	Second trimester No of subjects 12	Third trimester No of subjects 10	2–5 months post partum No of subjects 8
Coagulation time–min.				
glass tubes	15 (9–18)	16 (11–21)	16 (13–18)	14 (10–19)
plastic tubes	26 (19–35)	26 (18–33)	26 (20–32)	29 (17–43)
Platelet count per cu.mm	238,000 (172,000–430 000)	230,000 (156 000–348 000)	229 000 (130 000–362,000)	238,000 (172,000–272,000)
Platelet adhesiveness–%	28 (20–45)	34 (23–51)	25 (21–32)	30 (22–38)
Prothrombin consumption–%	6 (0–15)	7 (0–16)	8 (0–25)	7 (0–20)
AHF (f VIII)–%	116 (47–168)	171 (78–315)	257 (107–485)	80 (47–99)
Haemophilia B-factor (f IX)–%	115 (66–183)	117 (73–189)	114 (80–183)	96 (62–145)
Prothrombin+f VII+f X (P&P)–%	109 (76–150)	140 (104–183)	163 (105–230)	90 (59–108)

Factor V %	104 (87–124)	111 (99–126)	113 (90–128)	98 (73–107)
Fibrinogen—g/100 ml	0.36 (0.28–0.90)	0.41 (0.31–0.60)	0.50 (0.39–0.77)	0.27 (0.21–0.36)
Thrombin time	18 (16–23)	19 (14–22)	20 (18–20)	19 (18–20)
Fibrinolytic activity on unheated fibrin plates—mm²				
a) Plasma	44 (0–134)	0 (0–8)	3 (0–25)	33 (0–89)
b) Resuspended euglobulin precipitate	124 (4–474)	37 (0–90)	7 (0–65)	64 (16–99)
Plasminogen activity—%	113 (96–152)	131 (99–178)	150 (95–274)	100 (90–130)
Inhibitors of plasminogen activation by urokinase—%	109 (84–133)	97 (73–116)	123 (83–268)	122 (114–140)
Antiplasmin activity—%	127 (107–160)	177 (109–300)	167 (148–201)	105 (77–123)
Antiactivator activity—%	92 (45–142)	117 (82–152)	143 (89–238)	82 (65–91)

Determined in 7–8

Table II. *Coagulation and Fibrinolytic Studies Immediately Before and After Partus*

	Mean Values and Ranges in 12 Women					
	Before	1/2–3 hrs after	1 day after	2 days after	3 days after	4 days after
Coagulation time–min.						
glass tubes	15 (11–24)	16 (11–21)	14 (10–19)	13 (11–15)	13 (9–17)	12 (9–16)
plastic tubes	23 (17–27)	20 (14–28)	20 (12–26)	20 (16–26)	20 (16–24)	22 (15–30)
AHF (f VIII)–%	162 (77–500)	187 (94–480)	165 (93–360)	173 (93–410)	141 (95–185)	135 (90–198)
Haemophilia B-factor (f IX)–%	125 (70–185)	121 (58–150)	137 (82–253)	118 (75–175)	118 (82–165)	114 (90–145)
Prothrombin+f VII+f X (P&P)–%	169 (136–200)	165 (136–200)	144 (108–200)	162 (112–200)	162 (124–200)	138 (112–160)
Factor V–%	105 (58–120)	111 (95–141)	106 (77–131)	115 (101–127)	116 (95–143)	123 (108–160)
Fibrinogen–g/100 ml	0.56 (0 44–0 74)	0.59 (0 41–0 81)	0 55 (0 41–0 65)	0 60 (0 46–0 87)	0.57 (0 45–0 64)	0 60 (0 41–0.85)
Thrombin time (N.I.H units/ml)–sec	23 (16–27)	22 (15–27)	23 (18–31)	25 (17–32)	23 (16–26)	23 (21–25)
Fibrinolytic activity on unheated fibrin plates–mm						
a) Plasma	0 (0–0)	7 (0–30)	7 (0–25)	17 (0–102)	27 (0–83)	31 (0–89)
b) Resuspend. euglob prec.	7 (0–20)	35 (0–142)	28 (0–64)	61 (0–274)	72 (0–142)	57 (32–68)
Plasminogen activity–%						
Inhibitors of plasminogen activation by urokinase–%	87 (60–117)	94 (64–129)	105 (64–145)	114 (85–143)	123 (87–149)	–
Antiplasmi activity–%	112 (94–154)	113 (82–148)	113 (90–153)	112 (86–148)	111 (86–134)	118 (100–154)
Antiactivator activity–%	146 [illegible]	114 [illegible]	92 [illegible]	105 [illegible]	107 [illegible]	84 [illegible]

1964 *Todd* 1965 and others) and factor V to be unchanged (*Larrieu et al* 1952 *Alexander et al.* 1956 *Fresh et al.* 1956 *Talbert* and *Langdell* 1964 *Kasper et al.* 1964 *Rutherford et al.* 1964 *Todd* 1965 and others) Our findings concerning these factors are largely in agreement with these reports.

However some controversy remains regarding factors VIII and IX. It has been stated (*Fresh et al.*, 1956 *Ratnoff* and *Holland* 1959) that factor VIII is within normal limits during pregnancy but several more recent investigators have reported an increase not only in normal women but also in carriers of haemophilia A and v Willebrand's disease (*Strauss* and *Diamond* 1963 *Preston* 1964 *Rutherford et al.* 1964 *Talbert* and *Langdell* 1964 *Nilsson et al.* 1959 *Nilsson* and *Blombäck* 1962) *Todd* (1965) who performed coagulation studies on 26 women in various stages of pregnancy reported an increase in AHF in only 14 We found in all our investigated cases a marked increase in AHF which was apparent in the second trimester In the third trimester the AHF was always at least twice the initial value. Most authors have used AHF assays based on the partial thromboplastin time or thromboplastin generation test We used a method based on the ability of diluted plasma to correct the recalcification time of platelet-rich haemophilia A plasma. The haemophilia B factor was assayed in the same way using haemophilia B plasma as test substrate It may be argued that the high AHF levels do not reflect the true AHF activity but may include an unspecific thromboplastic effect. But the fact that we did not find high haemophilia B factor levels argues against such an assumption. Our finding concerning the AHF increase in pregnancy is in complete agreement with that reported by *Kasper et al* (1964)

Ratnoff and *Holland* (1959) *Rutherford et al* (1964) and *Kasper et al* (1964) found a marked increase in haemophilia B factor during pregnancy Other authors (*Koch* 1956 *Ross* 1963) found little or no increase of factor IX According to *Todd* (1965) factor IX may increase in some pregnant women but the lev ls reached are variable and never very high. In our patients there was no increase in haemophilia B factor activity

As far as we know the platelet adhesiveness has not been

studied systematically during pregnancy We found no changes in platelet adhesivenes during pregnancy

The fibrinolytic activity has been found to be reduced in the later months of pregnancy and to return to its original level very soon after delivery (*Biezenski* and *Moore* 1958 *Biezenski,* 1960 *Gillman Naidoo* and *Hathorn* 1959 *Shaper Macintosh Evans* and *Kyobe,* 1965) These authors used clot lysis assays. We measured the activity of plasma and resuspended euglobulin precipitate on unheated fibrin plates and found a decrease of the fibrinolytic activity apparent in the second trimester In the third trimester and also immediately before and after delivery practically no fibrinolytic activity was demonstrable. On the second day postpartum the fibrinolytic activity returned to normal *Brakman* (1966) who recently studied the fibrinolytic activity during pregnancy by assaying the activity of euglobulin precipitate from plasma and serum on fibrin plates found only a slight decrease of the activity *Brakman* stored the plasma samples at −20 C before use while we used fresh plasma that was added to the plates within 30 minutes of withdrawal of the blood (*Nilsson* and *Olow* 1962 a)

In agreement with *Brakman* (1966) we also believe that it is an activator of the fibrinolytic system which decreases during pregnancy

Only few reports are available on plasminogen levels during pregnancy *Naidoo Hathorn* and *Gillman* (1960) found it to be low but they did not assay the plasminogen selectively *Phillips* and *Skrodelis* (1958) who used a caseinolytic method with streptokinase for activation, found the total profibrinolysin to be increased during pregnancy *Ruckstuhl Bellet Sandberg* and *Gelber* (1962) also reported an increase in total fibrinolytic activity after streptokinase activation. *Shaper et al* (1965) and *Brakman* (1966) however found no difference in plasminogen levels between non-pregnant and pregnant women.

In the present study we have determined the plasminogen level by a clot method (*Nilsson Skanse* and *Gydell* 1957) According to this method the plasminogen level increased from a mean level of 113 per cent in the first trimester to a mean level of 150 per cent in the third trimester In a previous study

we determined the plasminogen level in pregnant women by a caseinolytic method (*Hedner* and *Nilsson* 1965). According to the caseinolytic method the mean plasminogen level in 15 pregnant women in the third trimester was 14.6 ACU/ml plasma compared with 9.7 ACU/ml in non-pregnant women ($p < 0.001$). It is difficult to explain why *Shaper et al.* (1965) and *Brakman* (1966) did not find an increase in plasminogen. *Shaper et al.* (1965) used a caseinolytic method and made estimations in 10 pregnant African women, but they did not state the stage of pregnancy. *Brakman* (1966) assayed plasminogen after destruction of the inhibitor by addition of cooled acetone to plasma. The precipitate was then dried and redissolved. After total activation with urokinase, the plasmin was assayed on heated fibrin plates. The plasminogen activity was thus expressed in square millimeters of lysed zones. This plasminogen method differs from other known plasminogen assays, and the results are difficult to compare with ours. Judging from our findings the plasminogen concentration is clearly increased during pregnancy.

Published reports of the behaviour of fibrinolytic inhibitors during pregnancy are also contradictory. *Guest* (1954) and *Phillips* and *Skrodelis* (1958) found an increase in plasmin inhibitor during pregnancy. *Naidoo et al.* (1960) believed that there was an increase in antifibrinolysin while *Blezenski* (1960) found the antifibrinolytic activity to be unchanged throughout pregnancy. In most of these studies it is, however, not clear whether determinations were made of antiplasmin, antiactivator, antistreptokinase or inhibitors of plasminogen activation. *Correll* and *Sjoerdsma* (1962) studied inhibition of urokinase-induced fibrinolysis by serum from patients with various diseases. Two pregnant women in the third trimester were investigated and the values found were normal in both. *Brakman* and *Astrup* (1963) found the capacity of the blood to inhibit urokinase or urokinase-induced fibrinolysis to increase selectively and significantly during pregnancy. They found no increase in true plasmin inhibitor. Our results are incompatible with those of *Brakman* and *Astrup*. In only one of 27 women was the inhibitory activity of plasminogen activation by urokinase increased while the anti-

plasmin activity and the antiactivator activity were moderately increased in all of them. These discrepancies may perhaps, have been due to the use of different assay methods. We determined the urokinase inhibitor (*Paraskevas et al.* 1962) in a test system with constant amounts of plasminogen, fibrinogen, urokinase and thrombin but with various concentrations of serum The lysis times were recorded. The inhibitory activity of the given serum sample was expressed as a percentage of that of a mixed serum sample from 10 normal individuals. Though significantly increased or decreased concentrations of antiplasmin can influence the determination and give falsely high or low values, there is no reason to suspect any such influence in our series for we found no changes in the level of urokinase inhibitor and only a moderate increase of the antiplasmin level. *Brakman* and *Astrup* (1963) mixed serial dilutions of plasma with urokinase and determined the fibrinolytic activity of each mixture on unheated and on heated fibrin plates. The lowest plasma concentration which completely inhibited the urokinase effect was determined It is possible that *Brakman* and *Astrup* determined the same inhibitory activity as we measured with our antiactivator assay

The mechanism responsible for the decreased fibrinolytic activity during pregnancy is unknown. According to *Brakman* (1966) the low activator activity during pregnancy cannot be explained by an interference of the high fibrinogen concentration or an increase in urine activator activation since normal or high activator activity has been observed both in association with a high fibrinogen level and an elevated inhibitory level. Some authors (*Bieenski* and *Moore* 1958 *Gillman et al.* 1959) have suggested that the decrease in fibrinolytic activity might be caused partly by an increase in inhibitory activity

Our findings thus appear to warrant the conclusion that the levels of P&P AHF and fibrinogen rise during pregnancy while the platelet count, the platelet adhesiveness and the levels of factor V and haemophilia B factor remain unchanged. There is a reduction of fibrinolytic activity and a rise in the levels of plasminogen antiplasmin and antiactivator during pregnancy

while the inhibitors of urokinase activation remain practically unchanged.

Owing to the increase in concentration of some coagulation factors and the decrease in fibrinolytic activity pregnancy has been considered as a hypercoagulable state implying an increased capacity to form fibrin and an increased tendency to thrombosis. So far no causal relationship has been demonstrated between intravascular thrombosis and alterations in any known coagulation factor (*Owren* 1965 *Johnson* 1965 *Erichson* 1965 *Wessler* and *Deykin* 1958) It must be recollected that the initial stage in thrombus formation is independent of plasma coagulation and depends on platelet function. According to *Owren* (1965) platelet adhesion tendency appears to be the most important link in the sequence of changes in the circulating blood contributing to the development of thrombosis. In the discussion of the question whether pregnancy predisposes to thrombosis it is important to bear in mind that no changes occur in platelet adhesiveness during pregnancy From clinical reports it also appears that *ante partum* thrombo-embolism is rare (*Taylor* 1965 *Breckenridge* and *Ratnoff* 1964 *Villasanta* 1965)

SUMMARY

The platelet adhesiveness and the components of the coagulation and fibrinolytic systems were studied in 27 women during different stages of pregnancy

The coagulation time the platelet count, prothrombin consumption and the platelet adhesiveness, the levels of factor V and factor IX and the thrombin time remained unchanged throughout pregnancy The values for P&P and fibrinogen gradually increased. A marked increase of AHF was demonstrated already in the second trimester and in the last trimester the AHF values had increased to at least 200 per cent.

The fibrinolytic activity decreased and practically no spontaneous fibrinolytic activity could be demonstrated in the third trimester On the second day postpartum normal fibrinolytic activity reappeared. The plasminogen antiplasmin and anti

activator activities showed a moderate increase during pregnancy The inhibitors of plasminogen activation by urokinase remained unchanged.

The increased level of fibrinogen remained unchanged during the first four days after delivery but the levels of AHF P&P and plasminogen fell by about 20–30 per cent 2–5 months after delivery the results of all the analysis were normal

REFERENCES

Alexander B Meyers L Kenny J Goldstein R, Gurewich V and *Grinspoon L.* New Engl. J Med. *254* 358 1956
Bierenski J J., J clin. Pathol. *13* 220 1960
Biezenski J J and *Moore H C* J clin. Pathol. *11* 306 1958
Brakman P Amer J Obstet. Gynec. *94* 14 1966
Brakman P., and *Astrup T* Scand. J. clin. Lab Invest. *15* 603 1963
Breckenridge R T and *Ratnoff O D* New Engl. J Med. 270 295 1964
Correll J T and *Sjoerdsma A.* Proc. Soc. exp. Biol. (N Y) *111* 774 1962
Cronberg, S., Nilsson I M., and *Silwer J* Acta med. scand *180* 43 1966
Erichson R. B. N Y St. J Med. *65* 1091 1965
Fresh J W., Adams H and *Morgan F M* Obstet. Gynec N Y *13* 37 1959
Fresh J W Ferguson J H and *Lewis J H* Obstet. Gynec. N Y 7 117 1956
Gillman T., Naidoo S S and *Hathorn M* Lancet ii 70 1959
Guest M M J clin. Invest. *33* 1553, 1954
Hedner U., and *Nilsson I M* Thromb Diathes. haemorrh *14* 545 1965
Johnson A. J., Fed. Proc. *24* 827 1965
Kasper C K Hoag, M S. Aggeler P M and *Stone S* Obstet. Gynec. N Y *24* 242, 1964
Koch F Klin. Wschr *34* 174 1956
Larrieu M J Soulier J P and *Minkowski A* Etud. néonatal. *1* 39 1952
Loeliger A. and *Koller F* Acta haemat. 8 157 1952
Nilehn J E., and *Nilsson I M* Scand. J Haemat. *1* 313 1964
Naidoo S. S Hathorn M and *Gillman T* J clin Path *13* 224 1960
Nilsson I M Björkman S E v Studnitz W and *Hallén A* Thromb. Diathes. haemorrh. *6* 177 1961
Nilsson I M and *Blombäck M* Thromb. Diathes. haemorrh 9 Suppl. 2, p. 103, 1963
Nilsson I M., Blombäck M and *v Francken I* Acta med scand. *159* 35 1957
Nilsson I M Blombäck M and *Ramgren O* Acta med. scand *170* 665, 1961

Nilsson *I. M., Blombäck M., Thilén A., and v. Francken I.* Acta med. scand. 115 357 1959
Nilsson I M., Krook, H., Sternby N.-H., Söderberg, E., and Söderström N Acta med. scand. 169 323 1961
Nilsson I M., and Kullander S., Acta obst. et gynec. scand. 46 286 1967
Nilsson I. M., and Olow B., Acta chir. scand. 123 247 1962
Thromb. Diathes haemorrh. 8 297 1962
Nilsson I M Skanse B., and Gydell, K., Acta med. scand. 159 463 1957
Owren P A., Ann. intern. Med 63 167 1965
Paraskevas M Nilsson I M., and Martinsson G., Scand. J. clin. Lab Invest. 14 138 1962
Pechet L and Alexander B New Engl. J Med. 265 1093, 1961
Phillips L L., and Skrodelis V J clin. Invest. 37 965, 1958
Preston, A. E., Brit. J Haemat. 10 110 1964
Ratnoff O. D Colopy J E., and Pritchard J A. J Lab. clin. Med. 44 408, 1954
Ratnoff O D and Holland, T R., Ann. N.Y Acad. Sci. 75 626, 1959
Ross *R. A* Amer J. Obstet. Gynec. 86 77 1963
Ruckstuhl, L Beller S Sandberg H and Gelber L Amer J. Obstet. Gynec 84 424 1962
Rutherford R. N Hougie C Banks A. L., and Coburn W A. Obstet. Gynec N.Y 24 886, 1964
Sharper A G Macintosh D M., Evans C M and Kyobe J Lancet II, 706, 1965
Strauss H S and Diamond, L. K., New Engl. J. Med 269 1251 1963
Talbert L M. and Langdell, R. D Amer J. Obstet. Gynec. 90 44, 1964
Taylor J J Postgrad. Med. J 41 80 1965
Todd M. E Mayo Clin. Proc. 40 370 1965
Wessler S., and Deykin D Circulation 8 1190, 1958
Villasanta U Amer J Obstet. Gynec. 93 142, 1965

Received on Oct. 11th, 1966

activator activities showed a moderate increase during pregnancy The inhibitors of plasminogen activation by urokinase remained unchanged.

The increased level of fibrinogen remained unchanged during the first four days after delivery but the levels of AHF P&P and plasminogen fell by about 20–30 per cent 2–5 months after delivery the results of all the analysis were normal

REFERENCES

Alexander B Meyers L Kenny J Goldstein R Gurewich W, and *Grinspoon L* New Engl. J Med *254* 358 1956

Bierenski J J J clin. Pathol. *13* 220 1960

Bierenski J J and *Moore H C.* J clin. Pathol. *11* 306 1958

Brakman P Amer J Obstet. Gynec. *94* 14 1966

Brakman P and *Astrup T* Scand J clin. Lab Invest. *15* 603 1963

Breckenridge R T and *Ratnoff O D* New Engl. J Med. *270* 298 1964

Correll J T and *Sjoerdsma A.* Proc. Soc. exp Biol. (N Y) *111* 274 1962

Cronberg, S Nilsson I M and *Silwer J* Acta med. scand. *180* 43 1966

Erichson R. B N Y St. J Med. *65* 1091 1965

Fresh J W., *Adams H.*, and *Morgan F M* Obstet. Gynec., N Y *13* 37 1959

Fresh J W Ferguson J H and *Lewis J H* Obstet. Gynec. N Y *7* 117 1956

Gillman T Naidoo S S and *Hathorn M* Lancet ii 70 1959

Guest M M J clin. Invest. *33* 1553 1954

Hedner U and *Nilsson I M* Thromb. Diathes haemorrh. *14* 545 1965

Johnson A. J Fed. Proc *24* 827 1965

Kasper C K Hoag, M S Aggeler P M and *Stone S* Obstet. Gynec N Y *24* 242, 1964

Koch F Klin. Wschr *34* 174 1956

Larrieu M J Soulier J P and *Minkowski A.* Etud. néonatal. *1* 39 1952

Loeliger A. and *Koller F* Acta haemat. *8* 157 1952

Nilehn J-E. and *Nilsson I M.* Scand. J Haemat. *1* 313 1964

Naidoo S S Hathorn M., and *Gillman T* J clin. Path. *13* 224 1960

Nilsson I M Björkman S E v Studnitz W and *Hallén A* Thromb. Diathes. haemorrh. *6* 177 1961

Nilsson I M. and *Blombäck M* Thromb Diathes. haemorrh. 9 Suppl. 2, p 103 1963

Nilsson I M Blombäck M and *v Francken I* Acta med. scand. *159* 35 1957

Nilsson I M Blombäck M and *Ramgren O* Acta med. scand. *170* 665, 1961

Nilsson I. M., Blombäck M., Thilén A. and v. Francken I. Acta med. scand. 115 357 1958
Nilsson, I. M. Krook, H. Sternby N.-H. Söderberg, E., and Söderström N. Acta med. scand. 169 323, 1961
Nilsson I. M., and Kullander S. Acta obst. et gynec. scand. 46 286, 1967
Nilsson I. M., and Olow B. Acta chir. scand. 123 247 1962
Thromb. Diathes. haemorrh. 8 297 1962
Nilsson I. M. Skanse B. and Gydell K., Acta med. scand. 159 463 1957
Owren P. A. Ann. intern. Med. 63 167 1965
Paraskevas, M. Nilsson I. M. and Martensson G. Scand. J. clin. Lab. Invest. 14 138 1962
Pechet L., and Alexander B. New Engl. J. Med. 265 1093 1961
Phillips L. L., and Skrodelis V. J. clin. Invest. 37 965 1958
Preston A. E., Brit. J. Haemat. 10 110 1964
Ratnoff O. D. Colopy J. E., and Pritchard, J. A., J. Lab. clin. Med. 44 408, 1954
Ratnoff O. D., and Holland, T. R. Ann. N.Y. Acad. Sci. 75 626 1959
Ross R. A. Amer. J. Obstet. Gynec. 86 77 1963
Ruckensahl, E. Beller S., Sandberg, H. and Gelber L., Amer. J. Obstet. Gynec. 84 424, 1962
Rutherford R. N. Hougie C., Banks, A. L., and Coburn W. A. Obstet. Gynec. N.Y. 24 886 1964
Shaper A. G. Macintosh, D. M., Evans C. M., and Kyobe J. Lancet II, 706, 1965
Strauss H. S. and Diamond, L. K., New Engl. J. Med. 269 1251 1963
Talbert L. M. and Langdell R. D. Amer. J. Obstet. Gynec. 90 44 1964
Taylor J. J. Postgrad. Med. J. 41 80, 1965
Todd M. E. Mayo Clin. Proc. 40 370, 1965
Wessler S. and Deykin, D. Circulation 8 1190 1958
Villasanta U. Amer. J. Obstet. Gynec. 93 142, 1965

Received on Oct. 11th, 1966

Nilsson I ga Marie and Kullander Stig, Acta obst. et gynec. scandinav. 46 286, 1967

From the Coagulation Laboratory (Prof Inga Marie Nilsson) and the Department of Obstetrics and Gynaecology (Prof Stig Kullander) Malmö General Hospital University of Lund Malmö Sweden

COAGULATION AND FIBRINOLYTIC STUDIES DURING USE OF GESTAGENS[1]

BY

INGA MARIE NILSSON AND STIG KULLANDER

Since the introduction of oral contraceptives hormones in the latter part of 1950 s a number of reports and much discussion have appeared on the occurrence of thromboembolic disorders in women treated with progestional steroids with or without additional oestrogens (*Jordan* 1961 *Conference* Chicago 1962 *Brook* and *Jackson* 1963 *McWilliam MacDonald* and *Lindsay* 1963 *Reed* and *Coon* 1963 FDA Report, 1963 *Minogue et al* 1963 *Schatz et al* 1964 *Müller* 1965 *Reutter Siebenmann* and *Wegmann* 1965 *Nevin Elmes* and *Weaver* 1965 *Cahal* 1965 and others) A number of reports are now available dealing with changes in blood coagulation factors and fibrinolytic activity during such therapy Although the results are often contradictory many authors have stated that the gestagen agents produce a hypercoagulable state

We studied the platelet adhesiveness and the components of the coagulation and fibrinolytic system in 27 women during different stages of pregnancy (*Nilsson* and *Kullander* 1967) Such data are necessary as reference for evaluation of changes occurring during the use of gestagenic hormones. In the present investigation we studied these factors in 32 women taking anovulatory drugs in contraceptive or therapeutic doses. Determination of the fibrinolytic activity developing in the arm after venous

[1] This investigation was supported by grants from the Swedish Medical Research Council.

stasis was also made before and after administration of oral contraceptives.

Methods

Collection of blood and assays of coagulation factors and fibrinolytic components. These assays were performed in the way described by *Nilsson and Kullander* (1967)

Clinical Material

A. Four women treated with large doses of gestagens (Enavid® Searle, in a dose of 4 tablets a day) for 2 1/2–6 months because of endometriosis, were investigated. Blood samples were taken twice before treatment, once or twice a month during treatment, twice just after treatment was stopped and then 2 to 5 times during the following 10 months. One (R.J.) of these patients became pregnant 9 months after the end of treatment. Blood samples were then taken in the first, second and third trimesters and again in the puerperium. The course in these 4 cases is illustrated in Figs. 1–4

B. Twenty-five normal, healthy women of childbearing age who for the purpose of contraception were using Anovlar® (Schering) 21 taken from the fifth to the twenty-fifth day of the menstrual cycle, were also investigated. When the blood samples were drawn, 12 women had been taking the pills for 2 months 8 for 12 months and 5 for 2 years. No samples had been obtained from these patients before treatment.

Fifteen healthy non-pregnant women of child-bearing age not using oral contraceptives served as controls. One woman (M.B.) was repeatedly studied for 1 year while she was using Anovlar and then again during a subsequent pregnancy (Figs. 5 a and b)

C. In 13 women we studied the fibrinolytic activity induced by venous stasis before and after 2 months use of Anovlar in contraceptive dose. Venous stasis of the arm veins was induced

One tablet contains 0.15 mg mestranol and 10 mg norethynodrel

One tablet contains 0.05 mg ethinyloestradiol and 4 mg norethisterone acetate

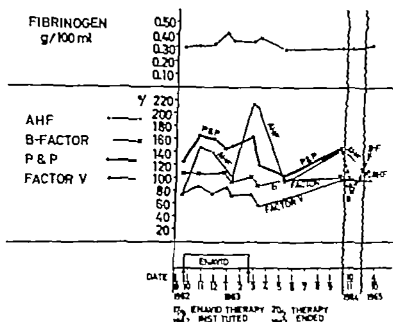


Fig 1 a. Coagulation studies in case G.B. during treatment with Enavid because of endometriosis.

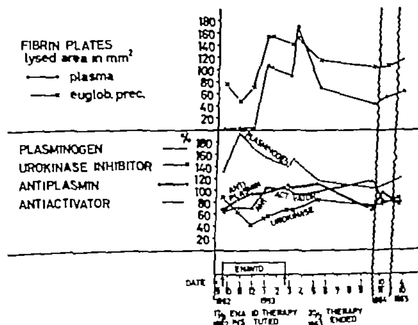


Fig. 1 b. Fibrinolytic studies in case G.B

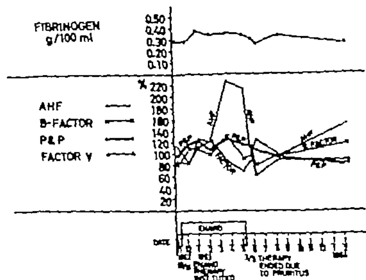


Fig. 2a. Coagulation studies in case L.S. during treatment with Enavid because of endometriosis.

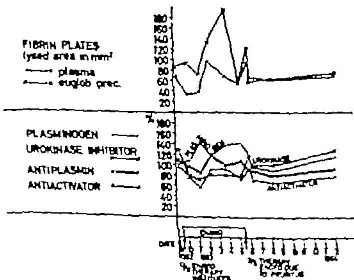


Fig. 2b. Fibrinolytic studies in case L.S.

Fig. 1 a. Coagulation studies in case G.B during treatment with Enavid because of endometriosis.

Fig. 1 b Fibrinolytic studies in case G B.

Fig. 2a. Coagulation studies in case L.S. during treatment with Enavid because of endometriosis.

Fig. 2b. Fibrinolytic studies in case L.S.

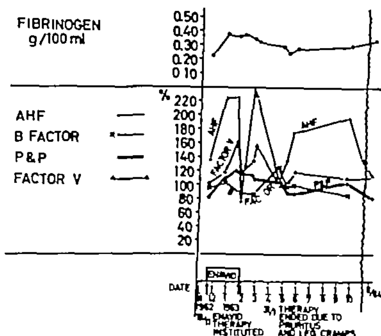


Fig. 3 a. Coagulation studies in case E.J during treatment with Enavid because of endometriosis.

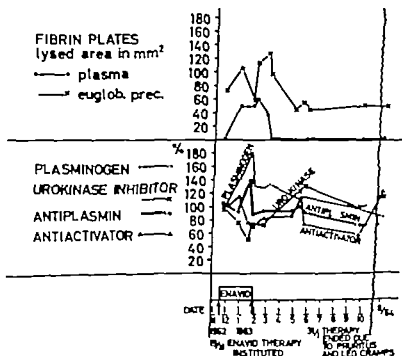


Fig. 3 b Fibrinolytic studies in case E.J

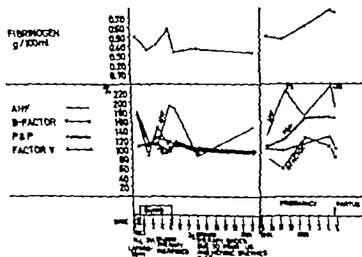


Fig. 4 a. Coagulation studies in case R.J. during treatment with Enavid because of endometriosis and during subsequent pregnancy

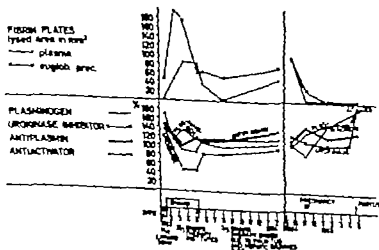


Fig. 4 b. Fibrinolytic studies in case R.J.

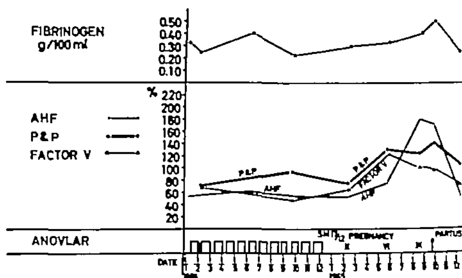
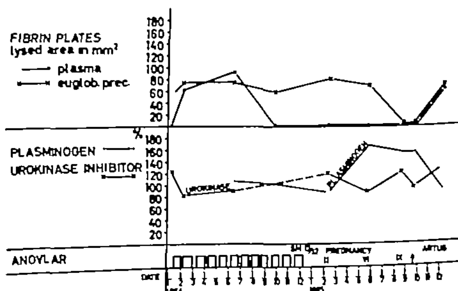


Fig 5 a. Coagulation studies in case M.B during Anovlar therapy and during a subsequent pregnancy



FIFg. 5 b Fibrinolytic studies in case M B.

for 15 minutes by means of a sphygmomanometer cuff with a pressure half-way between the systolic and the diastolic pressure of the person examined. Blood samples from a cubital vein were taken before application of the cuff and just before it was removed. The fibrinolytic activity of plasma and resuspended euglobulin precipitate was determined on unheated and heated fibrin plates (*Nilsson* and *Olow* 1962).

D. The plasma AHF was determined in a 32 year old carrier of haemophilia A (I.C.) before and after 10 months use of Anovlar. The AHF content of plasma and the Duke and Ivy bleeding times were determined in a 35 year old woman with severe v. Willebrand's disease before and after she had been taking Anovlar for 18 months.

The platelet adhesiveness was determined in a 33 year old woman with mild thrombasthenia before and after the use of Anovlar for 10 months.

Results

The results of the coagulation and fibrinolytic studies in the 4 women who received large doses of Enavid because of endometriosis are given in Figs. 1–4. The AHF (f. VIII) increased by about 100 per cent and the P&P (prothrombin+f. VII+f. X) fibrinogen and plasminogen by 20–60 per cent. In 2 of these patients a slight increase of factor V was noted. The haemophilia B-factor (f. IX) remained unchanged. In contrast to what is found in pregnancy, the fibrinolytic activity did not decrease. The inhibitors of plasminogen activation by urokinase decreased by 20–40 per cent. The antiplasmin activity and the antiactivator activity showed no significant changes. In one patient (R. J. Fig. 4) the values found for AHF, fibrinogen, factor V, plasminogen, antiplasmin and inhibitors of plasminogen activation by urokinase were high before treatment with Enavid therapy was started. These high values were expected because the patient had undergone laparotomy (when endometriosis was found) 8 days before she was placed on Enavid and because it is known that these factors increase postoperatively (*Olow* 1963, *Egeberg*,

1962 *Guest*, 1954) This patient became pregnant 16 months after Enavid had been withdrawn. It appears from Figs. 4 a and b that the changes in the coagulation factors occurring during the use of Enavid resembled those seen in the second trimester of pregnancy except that the use of the drug was not accompanied by any fall in fibrinolytic activity The inhibitors of plasminogen activation by urokinase remained unchanged in the samples drawn in the first, second and third trimesters but decreased during the use of Enavid. As mentioned in this patient the antiplasmin activity was increased when Enavid was instituted but returned to normal during further treatment. This also holds for the antiactivator activity These inhibitory activities increased during the pregnancy One patient (E.J) (Figs. 3 a and b) almost invariably fainted when the blood sample was being collected. The AHF values in this patient varied considerably from one occasion to another and were often very high. It is known that stress can increase the AHF activity (*Ingram* 1961) and it might help to explain the irregularity of the AHF values noted in this case.

The results of the analysis in the 25 women who had been taking Anovlar in a conventional contraceptive dose are given in Table I The AHF rose in only one of the women and then only slightly In 14 of the women the P&P remained unchanged in 10 it was 130–160 per cent and in one patient it was 192 per cent The patients with high P&P values had taken Anovlar for at least 6 months. In only 1 woman was the factor V increased and then only slightly In 4 women the fibrinogen was slightly increased. No increase occurred in the platelet count or adhesiveness. The spontaneous fibrinolytic activity and the content of inhibitors of fibrinolysis were normal in all of the 25 women. The mean plasminogen determined by a clot method (*Nilsson Skanse* and *Gydell* 1957) was higher in the Enavid group than in the controls. Thus in 8 of the 25 women studied the values ranged from 140–178 % In 10 of the women the plasminogen was also determined by the caseinolytic method (*Hedner* and *Nilsson* 1965) and corresponding results were obtained. One woman (M.B) was studied for 12 months during the use of oral contraceptives and also later during pregnancy (Figs. 5 a and b) During the use of the contraceptive there was only a

Table I. Coagulation and Fibrinolytic Studies in Normal Women With and Without Anovlar Therapy

	Anovlar Group mean values and ranges in 25 women	Untreated Group mean values and ranges in 15 women
Coagulation time—min.		
glass tubes	11 (8–15)	14 (10–19)
plastic tubes	16 (10–22)	29 (17–43)
Platelet count—per cu mm	212,000 (83,000–337,000)	238,000 (172,000–274,000)
Platelet adhesiveness—%	25 (16–42)	30 (22–38)
AHF (f VIII)—%	82 (40–168)	80 (47–99)
Haemophilia B-factor (f IX)—%	85 (48–185)	96 (62–143)
P&P—%	117 (89–142)	90 (59–108)
Factor V %	102 (84–138)	98 (73–107)
Fibrinogen—g/100 ml	0.31 (0.23–0.49)	0.27 (0.21–0.36)
Fibrinolytic activity on unheated fibrin plates—mm		
) Plasma	32 (0–146)	33 (0–89)
b) Resuspend euglob prec.	77 (0–179)	64 (16–99)
Plasminogen activity—%	128 (89–187)	100 (90–130)
Inhibitors of plasminogen activation by urokinase—%	89 (65–110)	122 (114–140)

slight increase of the P&P and fibrinogen, but marked changes occurred during the pregnancy

In the carrier of haemophilia A the AHF was 30 per cent before and 32 per cent after Anovlar therapy In the patient with Willebrand's disease the AHF values ranged from 5 to

Table II. *Fibrinolytic Activity of Blood Samples Taken at the End of 15 Min. Venous Stasis of the Arm Before and After 2 Month's Medication With Anovlar in 13 Women*

Case	*Before*				*After Enarid*			
	Unheated plates mm		Heated plates mm		Unheated plates mm		Heated plates mm	
	plasma	euglob. prec.	plasma	euglob. prec.	plasma	euglob. prec.	plasma	euglob. prec.
1	288	311	114	72	373	616	123	128
2	93	210	39	36	242	260	88	69
3	191	369	84	123	262	566	97	96
4	99	385	67	97	148	237	31	79
5	330	519	63	96	210	304	150	136
6	89	157	19	57	140	205	28	99
7	135	155	47	25	246	377	90	94
8	172	272	58	79	187	415	103	96
9	121	189	63	105	398	531	84	109
10	148	196	75	51	161	404	97	90
11	183	320	109	66	246	343	118	87
12	208	364	90	107	301	380	62	77
13	217	387	122	79	166	120	30	49
Mean	175	295	73	76	233	366	85	93

18 per cent before and from 10 to 20 per cent after Anovlar® treatment. The Duke bleeding time was > 30 minutes both before and after treatment. In the patient with thrombasthenia the platelet adhesiveness was 16 per cent before and 17 per cent after 10 months treatment with Anovlar. The prolonged Ivy bleeding time did not become shorter.

The results of the investigation in 13 women of the fibrinolytic activity induced by venous stasis before and after 2 months use of Anovlar showed no difference in activity before and after therapy (Table II).

Discussion

Treatment with oral contraceptive hormones induces a state which in some respects resembles that of pregnancy. It is well documented that pregnancy is accompanied by an increase in

the activity of several coagulation factors and by a decrease of the fibrinolytic activity. Thus, in a recent study (*Nilsson* and *Kullander* 1967) we found that the P&P, AHF and fibrinogen rose during pregnancy, while the platelet count, the platelet adhesiveness and the levels of factor V and haemophilia B-factor remained unchanged. There was a fall of fibrinolytic activity and a rise of the plasminogen, antiplasmin and antiactivator while the inhibitors of urokinase activation remained practically unchanged. Though wide agreement has been reached concerning the changes occurring in the blood during pregnancy, the reports on the effect of oral contraceptives on the coagulation mechanism and the fibrinolytic system are very conflicting.

Egeberg and *Owren* (1963) reported that Enavid caused an increase of the AHF (f. VIII) and a slight but significant increase of factor VII in 5 women studied during the first and second weeks of therapy. They noted no changes in the factor V or the fibrinogen level. According to *Rutherford et al.* (1964) treatment with Ortho-Novum significantly increases the prothrombin, factor VII, factor IX and the P&P. They found only a slight and inconclusive increase of factor VIII and factor V. In *Thomson* and *Poller's* (1965) series of 40 patients the use of oral contraceptives was accompanied by a significant increase of factor VII from the third month on. There was no elevation of the AHF. *Miller, Lee* and *Ritz* (1965) found in 25 women receiving progestin-oestrogen an increase of platelet count, P&P and fibrinogen level and a decrease of plasma proteolytic activity. The differences were, however, small. *Donayre* and *Pincus* (1965) studied 64 women taking Enavid. They found a slight increase of the prothrombin group and the fibrinogen level coexisting with an enhanced fibrinolytic activity. *Powell et al.* (1965) found that oral contraceptives had no significant effect on the prothrombin, factor VII, partial thromboplastin time, antifibrinolysin and fibrinolytic activity. *Mammen et al.* (1963) and *Sobroro et al.* (1963) found no significant changes in the coagulation and fibrinolytic system in women using Provest and Ortho-Novum, respectively. *Pilgeram* and coworkers (*Pilgeram et al.* 1964, *Amundson* and *Pilgeram*, 1964, *Pilgeram*, 1964) reported that Enavid therapy increased the plasminogen, fibrinogen

Table II *Fibrinolytic Activity of Blood Samples Taken at the End of 15 Min. Venous Stasis of the Arm Before and After 2 Month's Medication With Anovlar in 13 Women*

Case	*Before*				*After Enavid*			
	Unheated plates mm		Heated plates mm		Unheated plates mm		Heated plates mm	
	plasma	euglob. prec.	plasma	euglob prec.	plasma	euglob prec.	plasma	euglob. prec.
1	288	311	114	72	373	616	123	128
2	93	210	39	36	242	260	88	69
3	191	369	84	123	262	566	97	96
4	99	385	67	97	148	237	31	79
5	330	519	63	96	210	304	150	136
6	89	157	19	57	140	205	28	99
7	135	155	42	25	246	377	90	94
8	172	272	58	79	182	415	103	96
9	121	189	63	105	398	531	84	109
10	148	196	75	51	161	404	97	90
11	183	320	109	66	246	343	118	87
12	208	364	90	107	301	380	62	77
13	217	387	122	79	166	120	30	49
Mean	175	295	73	76	233	366	85	93

18 per cent before and from 10 to 20 per cent after Anovlar® treatment. The Duke bleeding time was > 30 minutes both before and after treatment. In the patient with thrombasthenia the platelet adhesiveness was 16 per cent before and 17 per cent after 10 months treatment with Anovlar The prolonged Ivy bleeding time did not become shorter

The results of the investigation in 13 women of the fibrinolytic activity induced by venous stasis before and after 2 months use of Anovlar showed no difference in activity before and after therapy (Table II)

Discussion

Treatment with oral contraceptive hormones induces a state which in some respects resembles that of pregnancy It is well documented that pregnancy is accompanied by an increase in

Judging from our analysis of the 25 women taking Anovlar in conventional contraceptive doses, the drug sometimes produced a slight increase of the P&P fibrinogen and plasminogen. But it had no significant effect on the other coagulation factors the platelet adhesiveness was not affected, and the fibrinolytic activity was not inhibited.

A point extensively discussed to-day is whether treatment with gestagens causes any changes in the coagulation factors that might be able to predispose to thrombosis. Although the reports concerning alterations in coagulation factors and fibrinolytic components during the use of anovulatory drugs are contradictory most authors like us, agree that the changes are not great Various changes in the circulating blood have been studied for any enhancing effect on the tendency to thrombosis. The results have however been inconsistent and conflicting, and there are only a few changes in the circulating blood which have definitely been shown to predispose to thrombosis The adhesion of platelets to injured endothelial cells in the vessel wall is the first step in the formation of a thrombus. There is evidence that an increased platelet adhesiveness predisposes to thrombosis (*Owren* 1965 *Hirsh* and *McBride* 1965 *Nilsson* 1966, and others) Judging from our findings, neither pregnancy nor the use of gestagens is accompanied by any increase in platelet adhesiveness. *Nilsson et al.* (1961) described a syndrome consisting of hyperfibrinogenaemia, absence of fibrinolytic activity and high content of inhibitor in the fibrinolytic system in association with recurrent venous thrombosis There was no decrease in fibrinolytic activity and no increase of the fibrinolytic inhibitors during gestagen treatment. It is known that venous occlusion causes a pronounced increase of fibrinolytic activity (Cliffton 1960) This increase is ascribed to the local release of activator from the vessel wall (Kwaan and MacFadzean 1956) It would therefore appear that variation in the content of such activators in the vessel wall may be of significance in the local dissolution of thrombi. We recently found that venous stasis failed to enhance the fibrinolytic activity in some patients with recurrent venous thrombosis (unpublished data) In the present

and the activity of plasma antithrombin. *Brehm* (1964) investigated the circulation and the blood coagulation in a large series of women using Lyndiol and demonstrated a shortening of the coagulation time and of the prothrombin time, an acceleration of thromboplastin generation and an increase of factor VII and plasminogen. Antithrombin III was reduced, but factor V and prothrombin showed no changes He observed an increase in fibrinolytic activity but no change in antiplasmin levels. In 59 women, who had used Norlestrin cyclically for 15 months to more than 2 years *Margulis et al* (1965) found an increase in the platelet count and the clot tensile strength and a decrease in thromboplastin generation and recalcification time of platelet rich plasma But differences were all small, and probably of no clinical significance and possibly close to the known variations of methods of evaluation

Pepper and *Lindsay* (1963) however found that Enavid had no effect on the mean platelet count. *Phillips et al* (1961) found 19-non-steroid compounds to produce a significant rise in profibrinolysin and fibrinolysin and a less marked increase in antifibrinolysin. In *Brakman* and *Astrup's* (1964) series of women who had been taking Enavid for 6 to 16 months the fibrinogen concentration was abnormally increased, but the plasminogen activity was the same as in the controls There was no increase in urokinase-induced fibrinolysis.

In most of the studies reported above the anovulatory drugs were administered in contraceptive dosage

It is apparent from the above review that the factors which most authors have found increased to a greater or lesser degree are factor VII AHF and fibrinogen. Most authors seem to agree that there is no decrease in fibrinolytic activity

In the 4 women treated with large doses of Enavid in our series the AHF P&P fibrinogen and plasminogen increased to about the same extent as that normally seen in the second trimester of pregnancy In 2 of these patients factor V also increased. The haemophilia B factor remained unchanged. No alteration was noted in the thrombin time There was no decrease in fibrinolytic activity and the inhibitors of the fibrinolytic system decreased by 20–40 per cent.

number of cases diagnosed as pulmonary embolism was noted. The number in the last year was approximately 5 times that in the first year. *Breckenridge* and *Ratnoff* (1964) have also stressed that unexpected death due to pulmonary embolism in otherwise healthy persons is not as rare as is widely supposed. *Winter* (1965) has recently compared the reported fatalities from idiopathic thromboembolism in Enavid users with those predicted from the population at risk in the years 1961 and 1963. Incidence data were obtained from Mortality Section, Division of Vital Statistics, National Center for Health Statistics. From his figures it is apparent that massive use of Enavid has not increased the incidence of thromboembolic disease in women.

SUMMARY

The platelet adhesiveness and the various components of the coagulation and the fibrinolytic systems were studied in 4 women undergoing long-term treatment with large doses of gestagens because of endometriosis, and in 28 women who had been taking gestagens for 2–24 months in an ordinary contraceptive dose. Two of the patients were studied first during gestagen treatment and later after they had become pregnant.

In the 4 women, who received large doses of Enavid, the levels of AHF, P&P, fibrinogen and plasminogen increased to about the same degree as seen in the second trimester of pregnancy. Factor IX remained unchanged. There was no decrease in fibrinolytic activity. The inhibitors of the fibrinolytic system decreased by about 20–40 per cent.

In 25 women who had received Anovlar in conventional contraceptive doses for 2–24 months, a slight or moderate increase of the P&P level was found in 10 women, of the fibrinogen level in 4 and of the plasminogen level in 8. Anovlar in anticonception dose had no significant effect on the other coagulation factors. The platelet count and the platelet adhesiveness was not affected. The fibrinolytic activity and the inhibitors of the fibrinolytic system were normal.

Anovlar anticonceptional therapy did not inhibit the fibrinolytic activity which develops after venous stasis.

investigation treatment with gestagens *had no inhibitory effect* on the fibrinolytic activity developing after venous stasis.

Pregnancy is associated with a much more pronounced increase of coagulation factors than that occurring during the use of gestagens but thrombosis is very rare during pregnancy (Villasanta 1965) In the light of the literature and observations made in the present investigation we feel that the changes found *in the circulating blood in association with the use of gestagens* does not predispose to thrombosis.

It must be stressed that changes in the vessel wall are of significant importance in the causation of clinical thrombosis. The possibility that the anovulatory drugs predispose to thrombosis by inducing changes in the vessel wall has to be left open. It might be mentioned that *Goodrich* and *Wood* (1964) reported *that progestins used as oral contraceptives may perhaps predispose* to venous thrombosis owing to decreased venous tone and decreased mean linear velocity of venous blood flow in the calf On the other hand *Brehm* (1964) investigated blood circulation in a large series of women taking Lyndiol The circulation of the blood showed no changes capable of promoting thrombosis—but, if anything, changes inhibiting it *Brehm* observed *no thrombophlebitis during any of the 794 cycles he studied* and therefore considered it warranted to conclude that oral contraceptive treatment does not cause an increased tendency to thrombosis.

As pointed out in the introduction the debate on the occurrence of thromboembolic disorders attending the use of contraceptive drugs has continued unabated. From 1961 to 1963 at least 350 incidences of thrombosis with or without embolism had been reported with 9 deaths in 31 embolic involvements (FDA-report, 1963) to which several have since been added. The clinical reports of many of these cases are incomplete There has also been much discussion about the significance of these findings *in view of the occurrence of similar episodes* in the female population of childbearing age at large In a recent study of 853 cases of pulmonary embolism studied by *Morrell Truelove* and *Barr* (1963) from 1952–1961 a pronounced rise in the

number of cases diagnosed as pulmonary embolism was noted. The number in the last year was approximately 5 times that in the first year. *Breckenridge* and *Ratnoff* (1964) have also stressed that unexpected death due to pulmonary embolism in otherwise healthy persons is not as rare as is widely supposed. *Winter* (1965) has recently compared the reported fatalities from idiopathic thromboembolism in Enavid users with those predicted from the population at risk in the years 1961 and 1963. Incidence data were obtained from Mortality Section, Division of Vital Statistics, National Center for Health Statistics. From his figures it is apparent that massive use of Enavid has not increased the incidence of thromboembolic disease in women.

SUMMARY

The platelet adhesiveness and the various components of the coagulation and the fibrinolytic systems were studied in 4 women undergoing long-term treatment with large doses of gestagens because of endometriosis, and in 28 women who had been taking gestagens for 2–24 months in an ordinary contraceptive dose. Two of the patients were studied first during gestagen treatment and later after they had become pregnant.

In the 4 women, who received large doses of Enavid, the levels of AHF P&P fibrinogen and plasminogen increased to about the same degree as seen in the second trimester of pregnancy. Factor IX remained unchanged. There was no decrease in fibrinolytic activity. The inhibitors of the fibrinolytic system decreased by about 20–40 per cent.

In 25 women, who had received Anovlar in conventional contraceptive doses for 2–24 months, a slight or moderate increase of the P&P level was found in 10 women, of the fibrinogen level in 4 and of the plasminogen level in 8. Anovlar in anticonception dose had no significant effect on the other coagulation factors. The platelet count and the platelet adhesiveness was not affected. The fibrinolytic activity and the inhibitors of the fibrinolytic system were normal.

Anovlar anticonceptional therapy did not inhibit the fibrinolytic activity which develops after venous stasis.

The changes found in the circulating blood in association with treatment with gestagens are not believed to predispose *per se* to thrombosis.

REFERENCES

Amundson B A and *Pilgeram L D* Thromb. Diathes. haemorrh. *10* 400, 1964
Brakman P and *Astrup T* Lancet *ii* 10 1964
Breckenridge R T and *Ratnoff O D* New Engl. J Med. *270* 298 1964
Brehm H Internat. J Fertil *9* 45 1964
Brook M H and *Jackson N J* Canad. Med. Med. Ass. J *89* 1094 1963
Cahal D A Lancet *ii* 1013 1965
Clifton E E Amer J Cardiol. *6* 476 1960
Conference Chicago Sept. 10 1962, Proceedings G.D Serale & Company
Donayre J and *Pincus G* Metabolism *14* 418 1965
Egeberg, O Acta med. scand. *171* 679 1962
Egeberg, O and *Owren P A*, Brit. med. J *1* 220 1963
FDA Report on Enovid JAMA *185* 776, 1963
Goodrich S M and *Wood E J* Amer J Obstet. Gynec. *90* 740 1964
Guest M M J clin. Invest. *33* 1553 1954
Hedner U and *Nilsson I M* Thromb Diathes. haemorrh. *14* 545 1965
Hirsh J and *McBride J A* Brit. med. J *2* 797 1965
Ingram G I C J Physiol. *156* 217 1961
Jordan W M Lancet *ii* 1146 1961
Kwaan H C and *MacFadzean A J S* Clin. Sci. *15* 245 1956
Mammen E F *Aoki N* *Oliveira A C* *Barnhart M I* and *Seegers W H* Internat. J. Fertil. *8* 653 1963
Margulis R *Ambrus J* *Mink I* and *Stryker J* Amer J Obstet. Gynec. *93* 161 1965
McWilliam R S *MacDonald A J* and *Lindsay I* Canad. med. ass. J *88* 1032, 1963
Miller S P *Lee S L* and *Ritz N* Metabolism *14* 398, 1965
Minogue W F *Halperin I C* *Soler Bechara J* *Varriale P* and *Flood F B* New Engl. J Med. *268* 1037 1963
Morrell M T *Truelove S C* and *Barr A* Brit. med. J *2* 830 1963
Müller P H Schweiz. med. Wschr *95* 1367 1965
Nevin N C *Elmes P C* and *Weaver J A* Brit. med. J *1* 1586 1965
Nilsson I M The Thule International Symposium on Stroke in Stockholm April, 1966
Nilsson I M *Krook H* *Sternby N-H* *Söderberg, E* and *Söderström N* Acta med. scand. *169* 323, 1961
Nilsson I M and *Kullander S* *46* 273 1967
Nilsson I M and *Olow B* Acta chir scand. *123* 247 1962

Nilsson I. M *Skanse* B., and *Gydell*, K., Acta med. scand. 159 463 1957
Olow B Acta chir scand. 126 197 1963
Owren P A Ann. intern. Med. 63 167 1965
Pepper H., and *Lindsay* S. Internat. J. Fertil. 8 467 1963
Phillips L. L., *Turksoy* R. N and *Southam*, A. L. Amer J. Obstet. Gynec. 82 1216, 1961
Pilgeram L. O Brit. med. J. 1 883, 1964
Pilgeram L. O *Amendion* B A. and *Lofgren* P E., Thromb. Diathes. haemorrh. 11 94 1964
Powell, L. C., *Guest* M., and *Bond*, T P Amer J. Obstet. Gynec. 93 167 1965
Reed D L. and *Coon*, W W New Engl. J. Med 269 622, 1963
Reutter F *Siebenmann* R., and *Wegmann* T Schweiz. med. Wschr 95 303, 1965
Rutherford, R. N *Hougie* C., *Banks* A. L., and *Coburn* W A Obstet. Gynec. N.Y 24 888, 1964
Schatz I. J *Smith*, R. F *Breneman*, G M and *Bower* G C. JAMA 188 493, 1964
Sobrero A. J *Fenichel* R. L., and *Singher* H. O JAMA 185 136, 1963
Thomson J M., and *Poller* L Brit. med. J 2 270, 1963
Villanueva U Amer J Obstet. Gynec. 93 142, 1965
Wynn L C Metabolism 14 422, 1965

Received on Oct. 11th, 1966

Felding, Carl, Acta obst. et gynec. scandinav. 46, 304 1967
From The Maternity Department (The late Professor Sune Genell and Professor Stig Kullander) Malmö General Hospital Sweden

OBSTETRIC ASPECTS IN WOMEN WITH NON INFECTIVE RENAL DISEASE

BY

CARL FELDING

Assessment of the obstetric prognosis in a woman with pre-existing renal disease is difficult. There are many reasons for this. Renal disease may run so symptom-free a course that it is not revealed until routine examination of the urine is undertaken e g in an ante-natal clinic and it may then be misinterpreted as toxaemia of pregnancy The classification of renal diseases varies, and they are often difficult to diagnose The condition of chronic pyelonephritis has been recognized as a clinical entity only in the past decade The definition of hypertension and its place in the symptomatology of the nephropathies varies. The criteria of toxaemia vary in the literature and assessment of the influence of pregnancy on the long term prognosis of renal disease is extremely difficult.

Assessment of perinatal mortality is somewhat easier but on the other hand the incidence of abortion and the indications for therapeutic abortion are often uncertain.

Much of the literature concerning these problems contains retrospective investigations of patients suffering from toxaemia and it is not inconceivable that such patients are more carefully questioned about their previous health than other maternity patients.

The social and geographical variations in different countries are probably of paramount significance but it is difficult for the reader of foreign literature to evaluate these.

In previous investigations, the present author (*Felding*, 1965) studied the prognosis in maternity patients with histories of urinary infection. The present investigation attempts to study the prognosis in patients who have had renal disease *without* known renal infection. The primary object is to account for the maternal morbidity and mortality prematurity and the perinatal mortality On the other hand, assessment of the maternal long-term prognosis and the further development of the renal disease after delivery are considered to be outside the scope of the present work.

Review of the Literature

It is apparent from numerous case reports that women with previous and possibly persisting severe renal damage can undergo normal pregnancy and confinement (*Fuchs* 1958 *Ziprick* 1954 *Wellen et al.* 1944 and *Herwig*, 1965) The most comprehensive of the extensive studies is that reported by *Mackay* (1963) This author subdivided the various forms of nephropathy into two main groups namely those with and without hypertension but at the same time commented on the uncertainty of renal diagnosis. Among 40 patients with persistent proteinuria he found an incidence of toxaemia of 35 per cent and foetal survival of 83 per cent. These women had normal renal function and were normotensive. In another group of 38 patients with proteinuria abnormal renal function and blood pressure of less than 175/110 foetal survival was 60 per cent and deterioration of the maternal renal disease was found in half of the cases. Twenty-eight of these 38 patients probably suffered from chronic nephritis. Among 25 patients with hypertension, foetal survival was 40 per cent and maternal renal status deteriorated in one third of cases.

Rauramo et al. (1962) studied 66 obstetric patients with a history of nephritis and found a perinatal mortality of 3 per cent. They considered that the decisive factor was the interval between the commencement of the renal disease and the subsequent pregnancy A short interval (less than three years) resulted in a poorer prognosis. Many authors consider that clinically healed glomerulonephritis or persistent proteinuria without other signs

of renal damage do not influence the course of pregnancy or the outcome of delivery (*Kaplan*, 1962 *Salou* 1942 *Reid* and *Teel* 1939 *Tillman* 1951 *Wilson* 1958 *Felding*, 1964) When proteinuria is combined with other signs of renal disease e.g. oedema, nitrogen retention and in particular hypertension, the obstetric prognosis is considered to be substantially worse (*Kaplan* 1962 *Kologlu* 1951 *Salou* 1942 *Tillman* 1951 *Wilson* 1958) In situations such as these, indications are frequently present for termination of pregnancy (*Dodds* and *Browne* 1940) or for induction of labour (*Hamilton* 1952 *Tillman* 1951)

Schrewe (1950) and *Gärtner* (1952) compared 34 patients with toxaemia and a history of nephritis with 666 other pregnant patients with no such history and found a definite difference in the maternal mortality and morbidity *Rudebeck* (1946) described the course of postnephritic parturition in 37 women without however reporting the obstetric details He compared these patients with a control group of 42 patients who did not have subsequent pregnancies and found no statistically significant difference between the two groups as regards the further course of the renal disease.

Werkö and *Bucht* (1956) detailed renal function investigations in 17 pregnant women with chronic diffuse glomerulonephritis and found no persistent deterioration in the renal disease after delivery although there was an increased risk of toxaemia in patients with hypertension.

Gibberd (1958) summarized the literature and his personal experience thus "When pregnancy occurs in a patient suffering from chronic Bright s disease the best prognosis for mother and child is in those patients whose only signs are chronic albuminuria and oedema When chronic nephritis is associated with a permanently high blood pressure the chance of a living child is so small and the dangers of pregnancy so great that it is necessary to advise against pregnancy The foetal mortality in chronic Bright s disease is generally stated to be about 50 per cent.

In his review Chronic renal diseases and pregnancy *Oken* (1966) summarized the relevant literature concerning the problem and the results were critically evaluated. The author gives a splendid summary of our present knowledge of the influences

of the various renal diseases upon pregnancy and delivery but did not report on any material of his own. *Oken* emphasized the difficulty of assessing the effect of pregnancy upon the immediate course of the renal disease and on the long-term prognosis.

The Influence of Renal Disease Upon Foetal Loss and Perinatal Mortality

Author Period	Diagnosis	No of patients	No of pregn.	Foetal loss	Perinatal mortality
Mackay 1957–60	Chron. renal damage				
	1 Normal renal function	46	46	17 %	
	2: Abnormal renal function				
	bloodpressure <175/110	38	38	39.5 %	28 %
	Bloodpressure >175/110	25	25	60 %	33 %
Rauramo 1930–57	Nephritis	66	116		3 %
Dodds, Browne bef 1940	Chronic nephritis	17	21	38 %	
Hamilton 1940–49	Chronic nephritis with hypertension	18	18	72 %	44 %
Kaplan 1922–58	Acute healed nephritis	17	34	9 %	3 %
	Chronic glomerulonephrit.	31	48	58 %	16 %
Kologlu bef 1951	Chronic nephritis	36	60	56 %	
Malbez bef 1955	Chronic nephritis				
	With hypertension	13	43		68 %
	Without hypertension	34	55		18 %
Reid, Teel bef 1939	Chronic glomerulonephritis	15	15	6 %	6 %
Felding 1932–42	Glomerulonephritis in childhood	41	67		3 %
Wroblewa bef 1956	Chronic nephritis with hypertension	10	10	80 %	71 %
Wilson 1932–58	Chronic nephritis				
	1. Proteinuria alone	18	35		6 %
	2. Proteinuria oedema, hypertension or RN ret.	8	18		39 %
Felding 1932–60 (Present material)	Acute healed glomerulonephritis	68	108		2 %
	Chronic renal damage	33	46		13 %

Material

The present study involves 123 patients with 189 deliveries and 191 infants.

The conditions for selection of the cases were as follows

1 Proteinuria and haematuria was present without demonstrable *bacteriuria or radiographic signs of pyelonephritis.*
2. Age at the commencement of the renal disease was 0–40 years.
3. All renal disease was diagnosed in hospital.
4 All deliveries, with one exception, took place in hospital.
5 With a few exceptions the renal disease had developed independently of pregnancy and delivery
6 Patients with diabetes were excluded.
7 All of the pregnancies continued until foetus was viable. Abortions and other pregnancies which were terminated before this stage were not included.

Nephrological data

Sixty-eight cases were classified as acute glomerulonephritis and of these 11 had been very mild with proteinuria, haematuria and frequently raised anti-streptococcal titre Twenty-nine patients showed a so-called typical course and 28 had severe symptoms such as anuria hypertension and nitrogen retention. Clinical restitution occurred in all 68 cases.

Thirty-three cases were classified as chronic nephropathy and *of these ten had reduced renal function and hypertension.* The remaining 23 cases had prolonged proteinuria and haematuria, but without definite signs of reduced renal function. Urography was undertaken in 12 patients. In 11 of these the results were normal and bilateral malrotation was demonstrated in one case.

Seventeen patients were classified as cases of orthostatic proteinuria.

Five patients had suffered from anuria (sulphonamide intoxication 2, complication of blood transfusion 1 criminal abortion 1 and unknown aetiology 1) All five patients had apparently recovered completely from the renal condition.

Obstetrical data

The obstetrical data concerning the 123 patients was obtained from the case notes in the maternity departments, mainly the Maternity Department in Malmö but also from other depart ments where the patients concerned were delivered.

At the time they developed the renal disease 106 patients were nulliparous and 17 had had at least one pregnancy

Age at onset of renal disease		
	<15 years	60
	15–30	61
	>30	2

Number of deliveries after onset of renal disease

72 patients with 1 delivery each		72 deliveries	73 infants
40	2 deliveries each	80	80
7	3	21	22
4	4	16	16
123 patients		189 deliveries	191 infants

Severe toxaemia (*Dieckmann's* classification 1952) occurred in 8 cases out of the total 189 deliveries i.e 4.2 per cent.

Prematurity (defined as birth weight under 2.500 g (5 1/2 lbs)) occurred in 10 out of 191 infants i.e 5.23 per cent.

Perinatal mortality 8 out of 191 infants i.e 4.2 per cent or 41 8 per thousand.

These figures do not differ greatly from normal but it is reasonable to subdivide the results into groups according to the nephrological data.

The 68 patients classified as acute glomerulonephritis are distributed according to parity thus

39 patients with 1 delivery each		39 deliveries	40 infants
23	2 deliveries each	46	46
3	3	9	10
3	4	12	12
68 patients		106 deliveries	108 infants

Severe toxaemia 1 per cent
Prematurity 3 7 per cent
Perinatal mortality 1 9 per cent *i.e* 19 per thousand.

The 33 patients who were classified as chronic nephropathy or chronic renal damage" are distributed according to parity thus

22 patients with 1 delivery each	22 deliveries	22 infants
9 „ „ 2 deliveries each	18	18
2 „ 3 „	6 „	6
33 patients	46 deliveries	46 infants

Severe toxaemia 15 per cent
Prematurity 13 per cent
Perinatal mortality 13 per cent *i e* 130 per thousand.

The 17 patients with orthostatic proteinuria were delivered of a total of 30 infants. Prematurity and perinatal mortality were nil and no patient had toxaemia.

The five patients with toxic renal damage were delivered of seven infants. None of the abovementioned complications occurred in this group

We have not attempted to follow the subsequent progress of the mother or to assess the influence of the pregnancy on the course of the chronic renal disease. On the other hand, it is of the greatest interest to attempt to elucidate the causes of foetal death and prematurity and to assess the cases most likely to give rise to these complications.

It is apparent from Tables I and II that the group of chronic nephropathy" despite its numerical inferiority is responsible for a high proportion of the premature deliveries and the perinatal mortality

Table I. *Clinical Details of the Eight Perinatal Deaths*

	Maternal diagnosis	Contributory circumstances	Birth weight	Cause of death	Subsequent fate of mother
KL b 1941	Chronic nephropathy	Premature delivery	1530	Prematurity	–
MT b 1917		Hypertension Premature delivery	1460	Ante-partum foetal death	Death in puerperium Cerebral haem.
GR b 1935			2570	Cardiac arrest	––
ALB b 1923		Premature delivery	1280	Prematurity	2 normal deliveries
BJ b 1940		Premature placental separation	1210	Prematurity	–
ALB b 1910		Toxaemia	1070	Ante-partum foetal death	Died 3 years later during preg. (Cerebral haem.)
ALB b 1907	Acute healed glomerulo-nephritis	Hypertension	3350	Ante-partum foetal death	––––
MBB b 1940		Premature delivery	1470	Prematurity	–––

Discussion

The present investigation confirms the findings of others and shows that renal disease which *has undergone* clinical recovery exerts little if any damaging influence upon subsequent pregnancies. There is no definite evidence that *persistent proteinuria* without other signs of renal damage is of any great significance. It is probable that accompanying hypertension is an adverse factor whether it is already present or if it develops during pregnancy.

The cases are characterized by considerable diagnostic uncertainty and, in this respect, the survey does not differ greatly from other reports. It may however be of value to the obstetrician when faced with a situation in which he has to assess the

Table II Clinical Details of Ten Premature Infants. Birth Weight Less Than 2500 g (5 1/2 lbs)

	Maternal diagnosis	Contributary circumstances	Birth weight	Condition of foetus	Subsequent fate of mother
KL b 1941	Chronic nephropathy	Premature delivery	1530	Dead	----
HT b 1917		Hypertension Prem. del.	1460	Dead	Death in puerperium
ALB b 1923		Premature delivery	1280	Dead	2 normal deliveries
BJ b 1940		Premature placental separation	1210	Dead	----
ALB b 1910		Toxaemia	1070	Dead	Died 3 years later during pregnancy
BN b 1925		Premature delivery	2350	Alive	----
MB b 1940	Acute healed glomerulo-nephritis	Premature delivery	14 0	Dead	----
LE. b 1937		Premature delivery	2460	Alive	Normal delivery 4 years later
GJ b 1933		Premature delivery	1500	Alive	----
VH b 1927		Premature delivery	2490	Alive	----

obstetric prognosis in a pregnant woman with previous or persistent nephropathy. It has been observed that a woman with nephropathy having an unsuccessful pregnancy can have a normal confinement at a later date. This was demonstrated by *Hamilton* (1952), *Mackay* (1963) and *Werkö* and *Bucht* (1956) and is confirmed by the present survey. To approach a solution of the problem, it is desirable to classify as far as possible each case of nephropathy occurring during pregnancy. It is important to separate urinary infections and pyelonephritis from other forms of nephropathy particularly in view of the favourable results

which *Rannevik* (1965) and others have obtained in the treat ment of bacteriuria during pregnancy

It seems probable that renal disease accompanied by hypertension involves a poor obstetric prognosis. This problem will be dealt with elsewhere.

It was not possible in this investigation to confirm the observation by *Rauramo* (1962) that the interval between the commencement of the renal disease and the subsequent pregnancy influences the prognosis. In 26 cases, the interval could, with certainty be determined to be less than three years. These 26 women were all delivered of living children and none of them developed severe toxaemia. In 45 women, the interval was over three years. Among these there were two perinatal deaths and, in addition, one case of severe toxaemia.

SUMMARY

The investigation involved 123 women with histories of renal disease With the reservations which are necessary in diagnostic classification of renal disease on the basis of review of the case histories, these 123 cases were distributed thus

68 cases of acute healed glomerulonephritis
33 cases of chronic renal damage or chronic nephropathy
17 cases of orthostatic proteinuria and
5 cases of toxic renal damage with anuria.

These women were delivered of 191 infants. The incidence of severe toxaemia was 4 2 per cent, prematurity (birth weight less than 2.500 g (5 1/2 lbs)) 5.23 per cent and of perinatal mortality (stillborn infants and infants dying within seven days of birth) 41.8 per thousand.

On subdivision of the cases according to the nature of the renal disease it became apparent that the incidence of the abovementioned complications was markedly greater in the group of chronic renal damage severe toxaemia occurring in 15 per cent, prematurity in 13 per cent and the perinatal mortality was 130 per thousand.

Acknowledgements

The author takes this opportunity of expressing his gratitude to Professor Jan Waldenström, The Medical Clinic Malmo General Hospital P Selander M.D The Paediatric Clinic, Malmo General Hospital G Widlund M.D The Gynaecological Clinic, Jönköping General Hospital Olof Nordenfelt M D The Medical Clinic Jönköping General Hospital and Professor N Alwall, The Renal Clinic Lund for access to the case histories.

REFERENCES

Dieckmann W J Toxemias of Pregnancy 2. ed. The C. V Mosby Company St. Louis 1952

Dodds G H and *Browne F J* Proc. roy Soc. Med. *33* 737 1940

Felding, C. Acta obstet. gynec. scand. *43* 141 1964

– Acta obstet. gynec. scand. *44* 304 1965

Fuchs F Ugeskr Laeg. *120* 905 1958

Gibberd G F Guy's Hosp. Rep. *107* 433 1958

Gärtner H Gynaecologia (Basel) *133* 210 1952

Hamilton H F H J Obstet. Gynaec. Brit. Emp. *59* 25 1952

Herwig, K R. Merrill J P Jackson R L. and *Oken D E.* Amer J Obstet. Gynec. *92* 1117 1965

Kaplan A. L. Smith J P and *Tillman A. J* Amer J Obstet. Gynec. *83* 1519 1962

Kologlu S Gaz. med. Fr *58* 375 1951

Mackay E V Aust. N Z J Obstet. Gynaec. *3* 21 1963

Millez P and *Fritel D* Sem. Hop. Paris (Arch. Soc. Biol. Med.) *31* 130, 1955

Oken D E. Amer J Obstet. Gynec *94* 1023 1966

Rannevik G Föredrag vid Medicinska Riksstämman 28/11 1965 Utgivet av AB Tika, Umeå

Rauramo L. Kasanen A. Elfving, K. and *Salmi H* Acta obstet gynec. scand. *41* 357 1962

Reid D E. and *Teel H M* Amer J Obstet. Gynec *37* 886 1939

Rudebeck J Clinical and Prognostic Aspects of Acute Glomerulonephritis Diss. Håkan Olsson, Lund 1946

Salou P Néphrites chroniques et gestation. Thèse Bosc frères, M., et Riou, L., Lyon, 1942

Schrewe B. Über die Beziehungen prägravider Nierenschädigungen zur Eklampsie drohenden Eklampsie Nephropathia gravidarum und zum Schwangerschaftshydrops. Diss. Münster 1950

Tillman A. J B. Med. Clin. N Amer 35 677 1951

Welles I Welsh, C. A. and Taylor H. C., J. clin. Invest. 23 742, 1944
Werkö L., and Bucht H., Acta med. scand. 153 177 1956
Wilson C., In Morris, N. F and McClure Browne, J C., (Ed.) A symposium on Non-Toxaemic Hypertension in Pregnancy J. & A. Churchill LTD London, 1958, p. 104
Wróblowa, W Pol. Arch. Med. wewnet. 26 1251 1956
Ziprick, H. F and Young, A. R., Amer J Obstet. Gynec. 68 1611 1954

Received on Sept. 7th, 1966

Author present address
Centrallasarettet
Linköping
Sweden

Erwald, Rolf Acta bst et gynec. scandinav 46, 316, 1967
From the Department of Surgery II (Head Hugo Rosenqvist M.D.) Södersjukhuset Stockholm Sweden

MAMMARY CARCINOMA AND PREGNANCY

BY

ROLF ERWALD

The expected child is often dismissed from the discussion of treatment of mammary carcinoma starting during pregnancy The pregnancy itself is often considered of interest only by virtue of the associated hormonal changes and their possible significance for cancer prognosis In a young family however the wish to have children is a factor that cannot be measured, but one that must always be taken into consideration by the surgeon, gynaecologist and radiotherapist in the rare case when a pregnant woman develops mammary carcinoma.

Report of two cases

In the last decade two cases of mammary carcinoma beginning in pregnancy have been treated at Södersjukhuset.

Case 1.—A woman aged 27 years She had been suffering from diabetes mellitus since childhood but was otherwise in good health. The first clinical evidence of the carcinoma was the discovery of palpable axillary metastases. At the time of mastectomy which was carried out in January 1964 the patient was in the third month of pregnancy The operation was performed by the technique that has been applied at this hospital since 1961 (*Rosenqvist* and *Erwald* 1963) Histological examination disclosed a deep central focus of highly differentiated intraductal carcinoma, the tumour being 2.5 cm in diameter and metastases without periglandular growth in all the axillary lymph nodes. The tumour was assigned to grade II (*Hultborn* and *Törnberg*, 1960) The patient received the usual postoperative radiotherapy and her subsequent course was uneventful. The pregnancy was not terminated but the child was born prematurely in the eighth month while the

mother was in diabetic coma. Foetal death from asphyxia followed within a few hours. The patient was advised against another pregnancy but she declared that she wanted to have children irrespective of any risk of deterioration in her condition, and she accordingly became pregnant. Because of the diabetes mellitus delivery was induced 3 weeks prematurely and a normal child was born in August, 1965. The child was fed from the remaining breast for 4 months. At the most recent check, in August 1965, there were no signs of local recurrence or metastases. This patient is now pregnant again, with expected confinement in October 1966.

Case 2.—Age 35 years. In December 1963, then in the second month of her fourth pregnancy she sought advice because 4 days previously she had felt tumour in the upper medial quadrant of one breast. Biopsy revealed a poorly differentiated intraduct adenocarcinoma, 7–8 mm across, with diffuse infiltration of the connective tissue and fat. Ten days later the breast and axillary nodes were removed. Histologic examination showed no residual tumour in the breast, but metastases with no evident periglandular growth were found in half a dozen axillary nodes. The tumour was classed as grade III. The usual postoperative radiotherapy was given and the recovery was uneventful. In the sixth month of pregnancy however there was a miscarriage, the cause of which was obscure. In the autumn of 1964 the woman became pregnant again but as she considered that she could not go through with it so soon after the treatment for the carcinoma she applied for and was granted, permission for a legal abortion. At the latest check in June 1966, the patient was in good health and there was no evidence of local recurrence or metastases.

The main problem in the discussion of the initial treatment of these two patients by the surgeons, gynaecologists and radiotherapists was whether or not the pregnancy should be interrupted. Both patients expressed eagerness to be able to have their children. The second patient, however declared that she would agree to interruption of the pregnancy if the physicians considered that it would improve her prospects of recovery from the carcinoma and if they recommended the measure. As this was not the case no abortion was performed.

Incidence and prognosis

The prognosis for a woman with mammary carcinoma beginning during pregnancy has, up to the last 15–20 years, been regarded as grave. Such cases are rare however and in a large collection from literature *White* (1954) found an incidence of 3 cases per

10 000 pregnancies. Still lower figures have been reported (*Betson* and *Golden* 1961 *Costarides* and *Theofanides*, 1963 *Robinson*, 1965) In a large series of cases of mammary carcinoma occurrence during pregnancy or lactation was found in between 2–3 per cent The incidence is considerably higher for younger than older women a figure of 14 per cent occurrence during pregnancy in a series of 550 cases of mammary carcinoma up to 35 years of age has been reported (*Treves* and *Holleb* 1958)

Of the many problems associated with such cases two will be dealt with here namely whether mammary carcinoma is affected unfavourably by pregnancy and whether a pregnancy subsequent to primary treatment of mammary carcinoma can affect the prognosis unfavourably

In their criteria of operability in mammary carcinoma *Haagensen* and *Stout* (1943) stated that occurrence during pregnancy or lactation categorically implied inoperability Since then, however *Haagensen* (1956) has modified his opinion in the light of his own and others experience Nevertheless on the basis of triple biopsy he judged only 50 per cent of his series as operable and surgically curable The triple biopsy however implies a narrow selection and consequently a higher percentage of good results The total survival in the whole group is of course, unaffected but if only cases with little if any spread are submitted to surgery the results for the operation group will be better than if wider indications are observed. Judged according to the usual clinical criteria the operability in pregnancy reported by various other authors is 60–70 per cent.

Even at the time of treatment the frequency of metastases in mammary carcinoma that has begun during pregnancy or lactation is extremely high. A survey of cases from the literature shows that there were axillary metastases in three quarters of them (Table I) Metastases in parasternal nodes are generally not reported in the published series probably because no such exploration has been carried out metastases in these nodes are, however extremely common. Out of 550 consecutive nonpregnant cases of mammary carcinoma in which *Handley* (1964) performed parasternal dissection of nodes as a routine measure he found metastases in 19–47 per cent, depending on the site

Table I. Prevalence of Axillary Metastases Found at Operation on Mammary Carcinoma Beginning During Pregnancy or Lactation

	No. of Cases of Mammary Carcinoma	Axillary Metastases No.	Per Cent
Harrington (1937)	92	78	85
White and White (1956)	25	18	72
Haagensen (1956)	31	25	81
Montgomery (1961)	70	52	74
Holleb and Farrow (1964)	133	98	7[illegible]
Peters and Meakin (1965)	130	97	75
Total	481	366	76

of the tumour They were found in more than one half of the cases of tumours with medial and central sites and with axillary metastases. Their presence was established in one quarter of the 2760 cases reported in the literature of mammary carcinoma undergoing surgical treatment with parasternal exploration (*Kholdin* 1965)

There is thus a higher frequency of axillary metastases among pregnant than non-pregnant women with mammary carcinoma this presumably applies also to parasternal metastases.

The prognosis from the published series of mammary carcinoma beginning during pregnancy or lactation varies widely (Table II) In cases in which there was clinical evidence that the disease was confined to the breast the 5-year survival showed a wide range 47–79 per cent In the case of *White's* (1955) review the figure was 22 per cent. For cases with metastases—that is the vast majority—the 5-year survival was as low as 7–18 per cent. Higher figures have been published for a few small series (*Hochman* and *Schreiber* 1953 *White* 1955)

Opinions are still divided as to whether a pregnancy in a woman with mammary carcinoma should be terminated to improve her prospects of recovery In his series *Westberg* (1946) found that termination of pregnancy appeared not to have any prognostic value. The same conclusion has been reached by *White* (1955) on the basis of a study of 1413 cases, including his

Table II. *Five-Year Survival as a Percentage of Women Operated on for Mammary Carcinoma During Pregnancy or Lactation*

	No. of Cases	Five-Year Survival (%) Axillary Metastases		
		Absent	Present	Total
Westberg (1946)	130	64	7	19
Harrington (1952)	136	65	9	23
Montgomery (1961)	70			34
Rosemund (1963)	37	79	13	33
Holleb and Farrow (1964)	119	65	17	31
Peters and Meakin (1965)	57	47	18	25
White (1955)	822	22	7	14

Review of literature

own and by several other authors (*Hochman* and *Schreiber* 1953 *Bunker* and *Peters* 1963 *Holleb* and *Farrow* 1964 *McManamy* 1964 *Peters* and *Meakin* 1965 *Robinson*, 1965) *Brown* (1960) maintained that either the mammary carcinoma is cured by primary treatment, and then termination of the pregnancy has no prognostic value at all or the disease has already become generalized and then the case is hopeless whether there is pregnancy or not. There are however many authors who recommend abortion (*Adair* 1953 *Lewison* 1954 *Betson* and *Golden* 1961 *Montgomery* 1961 *Groth* 1963 *Cade* 1964)

For women becoming pregnant *after* primary treatment for mammary carcinoma it is usually considered that the pregnancy does not worsen the prognosis (*White* 1955 *Atkins* 1964 *Holleb* and *Farrow* 1964 *McManamy* 1964 *More* and *Lewis* 1964 *Peters* and *Meakin* 1965) However others state that a treated mammary carcinoma *can* be reactivated by pregnancy (*Brown* 1960 *Cade* 1964) these authors therefore advise against a new pregnancy and recommend termination of a current one. In the group becoming pregnant after primary treatment for mammary carcinoma a selective factor operates in that those cases with the poorest prognosis are lost before they conceive again.

Discussion

Among the special circumstances on which the prognosis in mammary carcinoma beginning during pregnancy may depend are the age of the patient, the difficulty in palpating the physiologically altered breast and the modified hormonal pattern in pregnancy

The malignancy of the tumour is another unknown though highly significant prognostic factor (*Hultborn* and *Törnberg*, 1960 *Rosenqvist* and *Enwald* 1963) but as it is irrelevant to the present context it will not be dealt with in this discussion.

Age

The mean age of the cases of mammary carcinoma in Sweden is at present 56 years, and of those in which the disease begins during pregnancy or lactation about 34 years. Most authorities are agreed that age is a factor of significance the younger the patient, the poorer the prognosis irrespective of whether there is a simultaneous pregnancy (*Lewison* and *Trimble* 1953 *Treves* and *Holleb* 1958 *Goldenberg*, *Bellar Hayes* and *Lowry* 1961 *Groth* 1963 *Kleinfeldt Haagensen* and *Cooley* 1963) There is a body of opinion, however that youth does not necessarily imply a poorer prognosis (*Moore* and *Lewis* 1964)

Difficulties in physical diagnosis

The difficulty of detecting a small tumour in the breast that is physiologically altered by pregnancy or lactation may have great importance because of delay in diagnosis. Many estimates of this delay ha e been made. *Westberg* (1946) among others has put it at 2 3 months. *Bunker* and *Peters* (1963) found that only 7 per cent of their 150 cases received treatment within a month of the first symptoms. The swelling in the breast is often misinterpreted by both patient and physician as being part of normal changes of pregnancy and it may therefore go untreated for a long time The importance of adequate biopsies has often been stressed (*White* 1954 1955 *Austin* 1960 *McManamy* 1964 *Robinson* 1965)

Hormonal factors

Hormonal factors are considered to greatly influence mammary

carcinoma and particularly when the tumour begins during pregnancy or lactation

A decrease in the production of oestrogen by surgical or X-ray castration has been a common method of treatment for decades in cases of established local recurrence or widespread disease. A temporary remission has been found in 25–46 per cent of patients so treated (*Lewison* 1954 1962 *Person* and *Risholm*, 1959 *Kennedy Mielke* and *Fortuny* 1964)

The value of castration as a preventive measure is still a matter of debate Many authors have asserted that it can be effective up to 5 years after the menopause (*Treves* 1957 *Cole* 1962, 1964 *Paterson*, 1962 *Nissen-Meyer* 1964)

Though there is evidence to suggest that castration has a beneficial effect, it would seem that the cancerogenic effect of oestrogen is highly questionable It is well known that mammary carcinoma occurs more seldom in women that have had children and that have thus been exposed to high oestrogen levels for many months on at least one occasion *Wilson* (1962) has given oestrogen therapy to more than 300 women between 40 and 70 years some of them for 27 years Exposure totalled 2387 patient years the expected number of cases of mammary or genital carcinoma would then be 18 He found no cases and inferred that oestrogen does not promote carcinoma but in fact exerts a protective effect and accordingly suggested that it might be advisable to keep women endocrine rich and, consequently cancer poor throughout their lives the menopause would thus be eliminated. *Peters* and *Meakin* (1965) appear to hold a similar view when they state that from a biological aspect oophorectomy transfers a woman to the age group in which mammary carcinoma usually occurs

The fact remains however that the effect of oestrogen on mammary glands is due to or results in marked increase in vascularity There is therefore a greater likelihood of blood and lymph borne metastases and of stimulation of local tumour growth. Epithelial proliferation in the normal breast under the influence of oestrogen has also been recorded (*Haagensen* 1956)

Though progesterone is of significance in the psysiological alterations in the breast it is uncertain whether it has any effect

on mammary carcinoma. Nor is there any convincing evidence that chorionicgonadotrophins and pituitary hormones have an unfavourable effect on the disease.

Whether there is a risk that oral contraceptives exert an unfavourable effect in this respect is at present uncertain. The publication of large series with a long follow-up period is awaited with interest, particularly with regard to any change in the incidence of mammary carcinoma. That these agents have some effect on the normal breast is evident (*Stoll* 1964)

During pregnancy the secretion of cortisol is elevated and theories have been advanced that the excess can influence immunity mechanisms and so reduce the resistance to cancer cells (*Peters* and *Meakin* 1965)

Treatment

What treatment shall be given to a pregnant woman with mammary carcinoma? The answer to this question is probably that the same treatment should be given as if she had not been pregnant. If the carcinoma is judged to be operable the operation should be conducted in the usual way If it is deemed appropriate postoperative radiotherapy should also be given. *Westberg* (1946) found no evidence that an operation of this magnitude calls for termination of the pregnancy In both of our own cases reported above there was spontaneous termination of the pregnancy In the first case the premature birth probably resulted from the diabetic coma, but in the other case no explanation can be offered the postoperative radiotherapy cannot be excluded as a cause however

In the absence of metastases there is no reason to interrupt the pregnancy since it is not established that the prognosis is improved by this measure. If metastases have been found the prognosis is extremely poor but by no means hopeless. What to do about the pregnancy in such cases is often difficult to decide It must be borne in mind, however that in these cases, too it is not established that an abortion improves the prognosis or prolongs survival Consideration must then be given to any wish the patient may express to have the child, and to the husband s

carcinoma, and particularly when the tumour begins during pregnancy or lactation.

A decrease in the production of oestrogen by surgical or X-ray castration has been a common method of treatment for decades in cases of established local recurrence or widespread disease. A temporary remission has been found in 25–46 per cent of patients so treated (*Lewison* 1954 1962 *Person* and *Risholm*, 1959 *Kennedy Mielke* and *Fortuny* 1964)

The value of castration as a preventive measure is still a matter of debate Many authors have asserted that it can be effective up to 5 years after the menopause (*Treves* 1957 *Cole* 1962, 1964 *Paterson*, 1962 *Nissen Meyer* 1964)

Though there is evidence to suggest that castration has a beneficial effect, it would seem that the cancerogenic effect of oestrogen is highly questionable It is well known that mammary carcinoma occurs more seldom in women that have had children and that have thus been exposed to high oestrogen levels for many months on at least one occasion. *Wilson* (1962) has given oestrogen therapy to more than 300 women between 40 and 70 years some of them for 27 years Exposure totalled 2387 patient years the expected number of cases of mammary or genital carcinoma would then be 18 He found no cases and inferred that oestrogen does not promote carcinoma but in fact exerts a protective effect and accordingly suggested that it might be advisable to keep women "endocrine rich and, consequently "cancer poor throughout their lives the menopause would thus be eliminated. *Peters* and *Meakin* (1965) appear to hold a similar view when they state that from a biological aspect oophorectomy transfers a woman to the age group in which mammary carcinoma usually occurs.

The fact remains however that the effect of oestrogen on mammary glands is due to or results in marked increase in vascularity There is therefore a greater likelihood of blood and lymph borne metastases and of stimulation of local tumour growth. Epithelial proliferation in the normal breast under the influence of oestrogen has also been recorded (*Haagensen* 1956)

Though progesterone is of significance in the psysiological alterations in the breast it is uncertain whether it has any effect

Little is known about the malignancy of tumour cells, a factor that may well have an important bearing on the prognosis.

There is no proof that an abortion improves the prognosis in mammary carcinoma during pregnancy Nor is it established that pregnancy after primary treatment for mammary carcinoma increases the risk to the patient.

Greater consideration should be given to any wish of the parents to have the child.

REFERENCES

Adair F E Surg Clin N America 33 313, 1953
Atkins H T M Soc London 80 145 1964
Austin J R C Obst & Gynec 15 287 1960
Benson J J and *Golden, M L* Am J Obst & Gynec 81 718, 1961
Brown R N Surgery 48 662, 1960
Bunker M L and *Peters V M*, Am J Obst & Gynec 85 312, 1963
Cade S J Obst Gynaec Brit Comm LXXI, 341 1964
Cole M P J Int Coll Surg 38 539 1962
Brit J Surg 51 216, 1964
Contandes J and *Theofanides C* J Int Coll Surg 40 146 1963
Goldenberg, I S Bailar J C Hayes M A and *Lowry R* Ann Surg 154 397 1961
Groth F Ugesk Laeg 474, 1963
Haagensen C D and *Stout A P* Ann Surg 118 859 1943
Haagensen C D Diseases of the Breast, W B Saunders Co 1956
Handley R S Brit J Surg 51 206, 1964
Harrington S W J A M A 148 1007 1952
Ann Surg 106 690 1937
Hochman A and *Schreiber H* Obst & Gynec 2 268, 1953
Holleb A I and *Farrow J H* Acta Unio Internat Contra Cancrum, 20 1480 1964
Hultborn A and *Törnberg, B* Acta Radiol Suppl 196 1960
Kennedy B J Mielke P W and *Fortuny I E* Surg Gynec & Obst 118 24 1964
Kholdin S A Progr Clin Cancer 1 438, 1965
Kleinfeld G Haagensen C D and *Cooley E* Ann Surg 157 600, 1963
Lewison E F Internat Abstr Surg 99 417 1954
Obst & Gynec Survey 17 769 1962
Lewison E F and *Trimble I R*, J A M A 153 905, 1953
McManamy E P J Maine Med Ass 55 183 1964
Montgomery T L Am J Obst & Gynec 81 926, 1961
Moore S W and *Lewis R J* Surg Gynec & Obst 119 1253, 1964

attitude The patient and, especially her husband should also understand that there is a risk of recurrence, but that, on the other hand, there is no reason to believe that the progress of the disease would be retarded by terminating the pregnancy Many social factors will call for consideration. To summarize, if the patient and her husband wish to have the child come what may there is no reason to advise to the contrary even if the prognosis is judged to be grave.

In the series mentioned there is no evidence that subsequent pregnancy worsens the prognosis in a woman of fertile age treated for mammary carcinoma that, according to the clinical examination was restricted to the breast. Thus such patients need not be advised against subsequent pregnancy *Peters* and *Meakin* (1965) have even questioned whether a pregnancy is not to be recommended as a protective measure for a young woman that has been operated on for mammary carcinoma.

SUMMARY

The occurrence of mammary carcinoma during pregnancy is uncommon. Among the cases that come to surgical evaluation and treatment the proportion that is inoperable is greater and the incidence of axillary metastases is higher than in a normal mammary carcinoma series.

The prognosis is influenced by several factors.

Low age for a woman with mammary carcinoma during pregnancy may be a factor that worsens the prognosis.

The physiological changes in the breast during pregnancy complicate and possibly delay diagnosis. Palpation of the breasts should therefore be included in the examination of pregnant women, and biopsy of any suspicious lump in the breast is recommended.

In addition the increased vascularity of the breast would tend to promote spread of malignant cells

Hormonal factors are considered to have an unfavourable influence in mammary carcinoma during pregnancy but there is no definite proof that this is so

Little is known about the malignancy of tumour cells, a factor that may well have an important bearing on the prognosis.

There is no proof that an abortion improves the prognosis in mammary carcinoma during pregnancy Nor is it established that pregnancy after primary treatment for mammary carcinoma increases the risk to the patient.

Greater consideration should be given to any wish of the parents to have the child.

REFFERENCES

Adair F E Surg Clin N America 33 313 1953

Atkins H Tr M Soc London 80 145 1964

Austin Jr R C Obst & Gynec 15 287 1960

Betson Jr J and *Golden M L* Am J Obst & Gynec 81 718, 1961

Brown R N Surgery 48 862, 1960

Bunker M L and *Peters V M*, Am J Obst & Gynec 85 312, 1963

Cade S J Obst Gynaec Brit Comm LXXI, 341 1964

Cole M P J Int Coll Surg 38 539 1962

Brit J Surg, 51 216 1964

Costerides J and *Theofanides C*, J Int Coll Surg 40 146 1963

Goldenberg, I S Bailar J C Hayes M A and *Lowry R*, Ann Surg 154 397 1961

Groth F Ugesk Laeg 474 1963

Haagensen C D and *Stout A P* Ann Surg 118 859 1943

Haagensen C D Diseases of the Breast, W B Saunders Co 1956

Handley R S Brit J Surg 51 206, 1964

Harrington S W J A M A 148 1007 1952

Ann Surg 106 690 1937

Hochman A and *Schreiber H* Obst & Gynec 2 268, 1953

Holleb A I and *Farrow J H* Acta Unio Internat Contra Cancrum, 20 1480 1964

Hultborn A and *Törnberg, B* Acta Radiol Suppl 196 1960

Kennard B J Mueller P W and *Fortney L E*, Surg Gynec & Obst 118 524 1964

Kholdin S A Progr Clin Cancer 1 438, 1965

Kleinfeld G Haagensen C D and *Cooley E* Ann Surg 157 600 1963

Lewison E F Internat Abstr Surg 99 417 1954

Obst & Gynec Survey 17 769 1962

Lewison E F and *Trimble L R*, J A M A 153 905 1953

M Manamy E P J Maine Med Ass 55 160, 1964

Montgomery T L Am J Obst & Gynec 81 926, 1961

Moore S W and *Lewis R J* Surg Gynec & Obst 119 1253, 1964

Nissen Meyer R. Acta Unio Internat. Contra Cancrum 20 531 1964
Paterson R. J Royal Coll. Surg. Edinburgh 7 243, 1962
Persson B. H and *Risholm L.* Sv Läkaresällsk. sekt. för kirurgi förh. *XVII* 21 1959
Peters V M and *Meakin J W* Progr Clin. Cancer *1* 471 1965
Robinson D W J Obst. & Gynec. *9?* 658, 1965
Rosenqvist H and *Erwald R.* Opusc. Med. *8* 36 1963
Stoll B A. Brit. Med. J *5413* 875 1964
Treves N Cancer *10* 393 1957
Treves N and *Holleb A. I* Surg. Gynec. & Obst. *107* 271 1958
Westberg, S. V Acta obst. et gynec. scandinav *Suppl 4* 1946
White T T Ann. Surg. *139* 9 1954
– Surg. Gynec. & Obst. *100* 661 1955
White T T and *White W C.,* Ann. Surg. *144* 384 1956
Wilson R. A. J.A.M.A. *182* 327 1962

Received on Sept. 9th, 1966

Timonen, S. and Nieminen, U. Acta obst. et gynec. scandinav. 46, 327 1967
From Departments I and II of Obstetrics and Gynecology (Professor Aarno Turunen and Professor Paavo Vara) University Central Hospital Helsinki Finland

TUBAL PREGNANCY CHOICE OF OPERATIVE METHOD OF TREATMENT

BY

S. TIMONEN AND U. NIEMINEN

The frequency of ectopic pregnancy has steadily increased. This phenomenon has been observed both in Finland, e.g. by Apajalahti (1932) Parviainen (1943) Järvinen and Franzas (1954) and Kinnunen and Järvinen (1957) and in other parts of the world, e.g. by Webster et al. (1965) and Fielding (1965) In different series the frequency varies between 0.3 and 2.2 per cent. The increase in frequency has been attributed to the fact that patients seek medical aid more often than before, to improved diagnostic methods and to the introduction of antibiotics in the treatment of infections of the genital tract.

Material

At Department I and II of Obstetrics and Gynaecology Helsinki University Central Hospital, a total of 1085 ectopic pregnancies were treated during the years 1954–1965. Of these pregnancies 1067 were tubal and 18 ovarian. During the same period the total number of deliveries was 77 619. Thus the frequency of ectopic pregnancies was 1.4 per cent.

In Table I the patients are classified according to age and diagnosis. Attention is drawn to the fact that tubal rupture occurred in older age groups than unruptured tubal pregnancy and

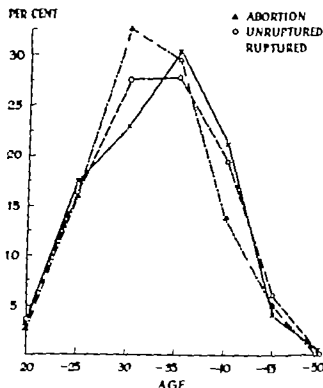


Fig. 1 Age distribution of different kinds of tubal pregnancy

tubal abortion This observation is demonstrated more clearly by the diagram in Fig. 1 The highest frequency of ectopic pregnancy was noted between 26 and 35 years. In the American series reported by Webster *et al* (1965) and Fielding *et al* (1965) the peak lies between 20 and 30 years which means that ectopic pregnancies occur about five years earlier in USA

Of the present 1085 extra-uterine pregnancies 568 were treated at Department I and 507 at Department II. These two Departments have adopted different principles of treatment. At Department I a more radical operative method has been applied, at Department II a more conservative method. In order to enable comparison between these two principles the material has in parts of this paper been treated as two separate series. Questionnaires were distributed by mail to all patients and 743 (68 6 per cent) replied.

Table I. *Age Distribution in 1085 Cases of Ectopic Pregnancy*

Age Group (Years)	–20	21–25	26–30	31–35	36–40	41–45	46–	No. of Cases
Diagnosis								
Ruptured	3.2	17.4	22.8	30.3	21.2	4.6	0.5	374
Unruptured	3.4	16	27.3	27.8	9.4	6.1	0.0	406
Abortion	2.8	5.8	32.6	29.5	24.0	5.3	0.0	287
Ovarian pregnancy	5.6	16.7	22.2	11.1	33.3	11.1	0.0	18
Total	3.2	18.5	27.1	28.7	18.9	5.4	.2	1085

Methods of treatment

As mentioned above at our two Departments both radical and conservative surgical measures have been used in the treatment of ectopic pregnancies

Radical treatment implies salpingectomy salpingo-oophorectomy and more extensive operations. Oophorectomy was performed only when absolutely necessary and total or subtotal hysterectomy very rarely In connection with salpingectomy limited cornual resection was usually performed.

Conservative treatment aims at preserving or reconstructing an injured tube if possible In particular this principle was applied if the other tube had previously been removed or was seriously damaged. We regard tubal resection longitudinal tubal section combined with evacuation of the ovum, manual expression of the ovum, tubal evacuation and tubal reimplantation as conservative operations. Often they were combined with the insertion of a transabdominal polyethylene catheter which was left in place for six weeks. During the first week 4 cc of a penicillin-hydrocortisone solution was injected daily through the catheter In addition, salpingostomy was performed in some cases, and when necessary salpingolysis and reposition of the uterus by various techniques were performed.

Table II shows the number of radical and conservative operations performed. The majority of operations (77 5 per cent) were radical.

In Table III the relative numbers (percentages) of the various

Table II *The Type of Operation Used in a Group of 1067 Cases of Tubal Pregnancy Conservative Operation Includes Tubal Section Expression of Ovum Tubal Resection and Tubal Reimplantation*

Type of Operation	"Radical"			"Conservative"	Total No. of Cases
	Salpingectomy Per Cent	Salpingo-oophorectomy Per Cent	Total Radical Per Cent	Per Cent	
Diagnosis					
Ruptured	78 9	8 0	86 9	13 1	374
Unruptured	57.4	16 5	73 9	26 1	406
Abortion	61 3	9.1	70.4	29.6	287
Total	66 0	11 5	77 5	22.5	1067

Table III. *Type of Conservative Operation in 240 Cases of Tubal Pregnancy*

Type of Operation	Section		Expression		Resection		Reimplantation per cent	Total No of Cases
	without Catheter per cent	with Catheter per cent	without Catheter per cent	with Catheter per cent	without Catheter per cent	with Catheter per cent		
Diagnosis								
Ruptured	6 1	14 3	0.0	0.0	49 0	24 5	6 1	49
	20.4		0.0		73 5			
Unruptured and abortion	18 3	32 5	17 3	3 1	20.9	6 3	1.6	191
	50.8		20.4		27.2			
Total	15.8	28.8	13.8	2.5	26 7	10.0	2.5	240
	44.6		16 3		36 7			

conservative operations may be seen. Resection was mostly performed in cases of tubal rupture (73 5 per cent) tubal section on patients with unruptured tubes (50 8 per cent) Catheters were inserted relatively frequently in both groups.

Results of surgical treatment

Fertility Table IV shows the frequency of post-operative pregnancies normal and abnormal. Complete data are available only in regard to those patients totalling 743, who replied to the questionnaire After conservative operation 53 0 per cent became pregnant after radical operation 49 3 per cent. Term pregnancies

Table IV *Proportions of Women who Became Pregnant after Operation as Percentages*

Type of Operation	Term Pregnancy	Term Pregnancy + Extra-uterine	Term Pregnancy Total	Only Extra-uterine	Extra-uterine Total	Abortion	Total	Total No. of Cases
Radical operation	27.2	2.0	29.2	9.5	1 5	0 6	49.3	558
Section	30	6.0	36.1	12.0	18.	13.3	61.4	83
Expression	20.7	3.4	24.1	20 7	24.1	20 7	65.5	29
Resection	17.6		17.6	8.8	8.8	11.8	38.2	68
Tubo-uterine implantation	20.0	0.0	20.0	20.0	20 0	0.0	40.0	5
Conservative operation total	23 8	3.2	27.0	2.4	15 7	14.1	53	185
Radical + conservative operation	26.4	2.3	28 7	10.2	12.5	11.4	50.2	43

Table V Proportions of Childless Women who *Became Pregnant after Operation as Percentages*

Type of Operation	Term Pregnancy	Term Pregnancy + Extra-uterine	Term Pregnancy Total	Only Extra-uterine	Extra-uterine Total	Abortion	Total	Total No. of Cases
Radical operation	28.8	3.8	32 6	8.8	1 5	5 6	48 9	160
Section	29.4	5 9	35 3	17.6	23 5	8.8	6 .8	34
Expression	26 7		26 7	33 3	33.3	3.3	73 3	5
Resection	17 5	.0	17 5	5	5.0	10	42.5	40
Tubo-uterine implantation			0 0	.0		0.0	0	
Conservative operation total	3 3		25 5	18 9	.1		54.4	90
Radical + conservative operation	26.8	3.2	30	2.4	5 6	7 2	49 6	250

were more frequent after radical operation, however Patients treated conservatively seem to be more likely to have complicated pregnancies (12.4 per cent against 9.5) and abortions (14 1 per cent against 10.6)

Table VI. *Subsequent Pregnancies in the Different Diagnostic Groups of Extrauterine Pregnancy as Percentages*

	Term Pregnancy	Term Pregnancy + Extra-uterine	Term Pregnancy Total	Only Extra-uterine	Extra-uterine Total	Abortion	Total	[illegible]
Diagnosis								
Ruptured	24.8	1 9	26 7	9.7	11.6	11 6	48.1	[illegible]
Unruptured	27 3	1 7	29.0	9.9	11.6	13.0	51.9	[illegible]
Tubal abortion	26.6	3 7	30.3	12.8	16 5	8.0	51.1	[illegible]
Total	26 3	2.3	28.6	10.6	12.9	11 2	50 3	[illegible]

On comparison of the results of the various conservative operations it is seen that complicated pregnancies occurred most frequently and term pregnancies relatively seldom (in 24.1 per cent) after expression of the ovum. The highest frequency of term pregnancies was noted after tubal section (36 1 per cent)

In the whole series 50 2 per cent became pregnant after operations of one kind or another Full term pregnancies occurred in 26.4 per cent.

In the group of women who were childless before operation 90 out of 250 (36 per cent) were treated by a conservative operative method (Table V) Of these 49 6 per cent became pregnant and 26 8 per cent had term pregnancies The distribution of complicated pregnancies was about the same as is seen in Table IV

In Table VI the postoperative pregnancies are classified according to the diagnosis of tubal pregnancy made before operation. In the tubal abortion group the frequency of recurrence of extra-uterine pregnancy was highest and the frequency of abortion lowest. In regard to subsequent term pregnancy differences between the various groups were slight the lowest frequency was noted in the group with tubal rupture

In Table VII the data are classified according to type of ectopic pregnancy and analysed from the standpoint of parity after operation. The frequency of postoperative pregnancies was highest in the ovarian pregnancy group Likewise the proportion of women who became pregnant was highest in this group

Table VII. *Number of Subsequent Term Pregnancies in the Different Types of Extra-uterine Pregnancy*

	No. of Pregnancies (Per Cent)					Total No. of Cases	Percentage of Cases with Subsequent Pregnancy
				3	≥4		
Diagnosis							
Ruptured	72.1	9	7.7	.8	.4	247	27.9
Unruptured and abortion	70.2	19.6	8.3	1.7	0.2	470	29.8
Ovarian pregnancy	53.8	30.8	3.4	0.0	0.0	3	46.2
Total	70.5	9.6	8.2	1.4	.3	730	29.5

Table VIII. *Fertility after Operation at Department I and II of Obstetrics and Gynaecology Helsinki University Central Hospital as Percentages*

Type of Operation	No. of Pregnancies	Term Pregnancy	Term Pregnancy + Extra-uterine	Term Pregnancy Total	Only Extra-uterine	Extra-uterine Total	Only Abortion	Total No. of Cases
			Dept I of Obst. & Gyn.					
Radical operation	52.4	28.8	1.5	30.4	8.9	10.4	8.3	326
Conservative operation	49.2	20.3	7	22	10.2	.9	18.6	59
Total	5 9	27.5	.6	29.1	9.1	10.6	9.9	385
			Dept II of Obst. & Gyn.					
Radical operation	50.4	25.4	6	27.8	9.5	2.1	2.5	232
Conservative operation	48.8	24.8	4.0	28.6	3.5	7.5		126
Total	49.2	24.9	3.	27.9	1.9	4		358

Table IX. *Proportion of Patients with Term Pregnancy after Radical and Conservative Operation at Department I and II of Obstetrics and Gynaecology*

	Total No. of Cases	Answered	"Radical" Per Cent	"Conservative" Per Cent	Total Per Cent
Dept I of Obst. & Gyn.	368	385	30.4	22	29
Dept II of Obst. & Gyn.	507	358	27.2	30.4	27.9

Table X. *Frequency of Extra-uterine Pregnancies after radical or Conservative Operation at Departments I and II of Obstetrics and Gynecology*

	Total no of Cases	Answered	"Radical" Per Cent	"Conservative Per Cent	Total Per Cent
Dept. I of Obst. & Gyn.	568	385	11 7	11.9	11.7
Dept II of Obst. & Gyn.	507	358	12.1	17 5	14.0

Table XI *Frequency of Abortions after Radical and Conservative Operation at Departments I and II of Obstetrics and Gynecology*

	Total No. of Cases	Answered	"Radical" Per Cent	"Conservative Per Cent	Total Per Cent
Dept. I of Obst. & Gyn.	568	385	20.2	28.8	21.6
Dept. II of Obst. & Gyn.	507	358	22.4	21.4	22.1

This group was too small, however for statistical evaluation of the results.

Differences between Departments I and II When the operative results of the two Departments are compared, it is seen that over one-third of all operations performed at Department II were conservative, whilst a conservative method was used in only one-seventh of cases at Department I Term pregnancies occurred more often at Department I (Tables VIII and IX) and ectopic pregnancies less frequently than at Department II (Tables VIII and X) A difference is also discernible in regard to the total frequency of abortions (Tables VIII and XI)

The age factor Postoperative pregnancies (deliveries and abortions) were most frequent in the age groups 26–35 years (Table XII) As could be anticipated, repeated pregnancies were most frequent in the younger age groups ($<$ 26 years)

Recurrent ectopic pregnancies occurred most often between the ages of 26 and 30 years (Table XIII)

Table XII. *Percentage Distribution According to Age and Number of Postoperative Pregnancies*

Age Group (Years)	—20	21—25	26—30	31—35	36—40	41—45	46—	No. of Cases
pregnancy	5	0.9	26.1	3 4	24 0	6 9	0.2	421
pregnancy	2.	8 0	32.3	28 6	14.8	4	0.0	189
pregnancies	7.1	28.2	35 3	20.0	8.2	1.2	0.0	85
> 3 pregnancies	8.0	36.0	20	26.0	10.0	0.0	0.0	50
Total	3	16 5	27 1	28 7	18 9	5.4	0.2	745

Table XIII. *Age Distribution of the Patient with Postoperative Extra-uterine Pregnancies Per Cent*

Age Group (Years)	—20	21—25	26—30	31—35	36—40	41—45	46—	No. of Cases
Postoperative extra-uterine pregnancies	0.0	17.9	43	25 3	1 6	1 1	0.0	95
Whole material	3 2	6 5	27.1	28.7	18 9	5.4	0.2	1035

Table XIV *Pelvic Pain after Radical and Conservative Operation*

Type of Operation	No Pains	Less than before Operation	No Change	More Pain than before Operation	Can't Say	Total No. of Cases
Radical operation	46 8	17 7	2.1	3	0.5	554
Conservative operation	43 3	6.	9.4	16.1	5	80

Postoperative pelvic pain An increase in pelvic pain after operation was more often noted in the patients treated conservatively (Table XIV) Abatement was slightly more common among those subjected to radical surgery

Discussion

In the present study the frequency of ectopic pregnancies corresponds to the figures previously indicated in the literature The highest frequency was noted between 26 and 35 years,

which is somewhat later than in certain American series, for instance In Finland normal pregnancies also occur later than in the USA and the Central European countries.

The fact that tubal rupture was found to be more frequent than unruptured tubal pregnancy and tubal abortion in the older age groups is not readily accounted for The lowering of tissue elasticity with increasing age seems to afford a possible explanation. It may also be assumed that the older patients have experienced various kinds of abdominal pain for some length of time and therefore postpone seeking medical aid, so that rupture occurs before any surgical intervention is possible.

In the present series the most radical operative methods were seldom used, salpingo-oophorectomy for instance, being performed in only 11 5 per cent of cases. By contrast, salpingectomy was frequently performed *i e* in 66 per cent.

Conservative operations were only performed in 22 5 per cent cases Even if a conservative method was to be regarded as preferable, it is not practicable in the majority of cases, since the tube is often damaged to such a degree that it cannot be reconstructed. There are no multiparæ or patients approaching the climacteric among the group who were treated conservatively since a further pregnancy was not desired in these cases. *Nonetheless in regard to the number of conservative operations* performed at Departments I and II respectively a clear difference is discernible At Department II a conservative method was used in about one-third of all cases against about one-seventh at Department I The fact that a conservative method was used in as many as 36 per cent of cases in the group of childless women shows moreover that the choice of method was determined by the situation if possible Although the present material is limited, the results offer a sufficient basis for comparison of the different operative methods. The fact that different principles of operative treatment have been applied at Departments I and II lends additional interest to this comparison.

After operation 50 2 per cent of the patients became pregnant. In the series of Järvinen and Kinnunen (1957) which was collected at the same hospital during the years 1945–1951 the corresponding figure was 39 per cent. Mention may further

be made of the following results reported in the literature Dougal (1927) 60 per cent, Apajalahti (1932) 53.1 per cent Mayo and Strassmann (1938) 36 9 per cent. In the present series postoperative term pregnancies were more frequent among the patients treated radically than among those who received conservative treatment, the frequency figures being 27 2 and 23.8 per cent, respectively The ratio was the same among the childless women, in whom every attempt was made to preserve fertility term pregnancies followed conservative operation in 23.3 per cent, and radical operation in 26 8 per cent. In the literature the frequency figures for term pregnancies after operative treatment of ectopic pregnancy vary between 15 and 30 per cent (Järvinen and Kinnunen, 1957 Giovanni and Wirtz, 1962 Grant, 1962) On the basis of the abovementioned results a radical method appears to be preferable.

In the present series recurrent ectopic pregnancy was diagnosed in 12 5 per cent (after radical operation in 11 5 per cent, after conservative operation in 15.7 per cent) Mayo and Strassmann (1938) reported recurrences in 4 per cent, Siegler (1945) in 5 per cent, Järvinen and Kinnunen (1957) in 11 per cent and Grant (1962) in 5 per cent. Thus, the frequency of recurrent ectopic pregnancy is markedly higher in the present series than in the series of other authors. After conservative operation abortions too were more frequent than after radical operation. The higher frequency of ectopic pregnancies following conservative operation is readily understandable but the difference in the frequency of abortions is unexpected. Perhaps the changes in the genital tract caused by the treatment of the tube are so radical that the persistence of even an intrauterine pregnancy is rendered difficult. This view is supported by the fact that postoperatively the patients treated conservatively xperienced more abdominal pain than the patients treated radically Perhaps uterine motility is disturbed by a damaged tube which is not removed.

Expression of the ovum seems to be the method leading to the most untoward effect, since abortions and recurrent ectopic pregnancies occurred more often after this operation than after any other On squeezing, the tube is obviously not completely n [illegible]

evacuated, and the remaining placental tissue causes adhesions leading to complications in subsequent pregnancies. This method of treating pregnancies in the ampulla of the uterine tube should be abandoned.

The poorer results in the group treated conservatively raises the question of whether this method can be recommended at all. On the whole its advantages are questionable but in certain cases it must be regarded as the method of choice Radical treatment does not seem to be justified in childless women with the contralateral tube severely damaged or completely destroyed. In regard to these, the increased risk of complications is not decisive when weighed against the chance of pregnancy In all other cases it appears that a radical operation may be recommended. In the present series the best results were noted after longitudinal tubal section (full term pregnancies in 36.1 per cent) Hence this operation may be regarded as the best conservative method available.

SUMMARY

1 A series of 1085 ectopic pregnancies is reported, particular attention being paid to the operative method used.

2 Of the whole series 77 5 per cent were treated by radical operation (mainly salpingectomy) The proportion of patients treated by conservative operation (mainly tubal section in combination with the introduction of a polyethylene catheter) was one-third at Department II of Obstetrics and Gynæcology and one-seventh at Department I of Obstetrics and Gynæcology

3 Questionnaires were answered by 743 patients. Of those treated conservatively 53 per cent had become pregnant, of those treated radically 49 3 per cent.

4 Of the patients undergoing radical operation 30 4 per cent had normal term pregnancies. The corresponding figure for the patients treated by conservative surgery was 27 2 per cent. In the latter group the frequency of tubal and intra uterine abortion was higher than in the group treated radically

5. From the standpoint of fertility longitudinal tubal section was the conservative operation yielding the best results (36 1 per cent) This operation was completed by the insertion of a transabdominal polyethylene catheter Postoperatively irrigation with a penicillin-hydrocortisone solution was performed.
6. Postoperative pains were more frequent among the patients undergoing conservative surgery
7. Conservative operation is recommended only in cases of sterility in which the contralateral tube is destroyed.

REFERENCES

Apsitalakn A Acta obst. et gynec. scandinav 12 329, 1932
Dougal D Brit. M. J 2, 974, 937
Fielding, W Kennedy R. and Gillies R. Obst. & Gynec. 26 702 1965
Giovanni L. and Wertz L., Ref· Grant, A. Clinical Obst. and Gyn. 5, 881 96
G ant A Clinical Obst. and Gyn. 5, 861 1962
Jarvinen P A. and *F ausas B.*, Nord. Med. 52, 1438 1954
Kristensen O and Järvinen, P A., Internat. J of Fertility 2 13 957
Mayo C W and Strassmann E O Surg. Gynec. & Obst. 67 46 1938
Permanen S Duodecim 59 4 1943
Siegler S L New York J Med. 45 974 945
Webster H Barclay D and Fischer C. Am. J Obst. & Gynec. 92 23, 965

Received on Aug 30th 966

evacuated, and the remaining placental tissue causes adhesions leading to complications in subsequent pregnancies. This method of treating pregnancies in the ampulla of the uterine tube should be abandoned.

The poorer results in the group treated conservatively raises the question of whether this method can be recommended at all. On the whole its advantages are questionable but in certain cases it must be regarded as the method of choice Radical treatment does not seem to be justified in childless women with the contralateral tube severely damaged or completely destroyed. In regard to these the increased risk of complications is not decisive when weighed against the chance of pregnancy In all other cases it appears that a radical operation may be recommended. In the present series the best results were noted after longitudinal tubal section (full term pregnancies in 36.1 per cent) Hence this operation may be regarded as the best conservative method available.

SUMMARY

1 A series of 1085 ectopic pregnancies is reported, particular attention being paid to the operative method used

2 Of the whole series 77 5 per cent were treated by radical operation (mainly salpingectomy) The proportion of patients treated by conservative operation (mainly tubal section in combination with the introduction of a polyethylene catheter) was one-third at Department II of Obstetrics and Gynæcology and one-seventh at Department I of Obstetrics and Gynæcology

3 Questionnaires were answered by 743 patients. Of those treated conservatively 53 per cent had become pregnant of those treated radically 49.3 per cent.

4 Of the patients undergoing radical operation 30 4 per cent had normal term pregnancies. The corresponding figure for the patients treated by conservative surgery was 27 2 per cent. In the latter group the frequency of tubal and intrauterine abortion was higher than in the group treated radically

of oxytocin. The patient is asked to blow the contents of the rhinyle into the nose as a result of which the Partocon finds its way exclusively into the nasopharynx and is there resorbed. The dose recommended by the factory on the basis of an exclusively clinical study of *Borglin* (1962) is 5 I.U every 15 minutes. The effect gained should be a guide for the time interval and the size of the next dose It is claimed that it is seldom necessary to administer a dose of more than 20 I.U

In 22 pregnant patients intranasal Partocon was used to induce labour while measuring the intra-uterine pressure through an open saline filled vinylcatheter that was introduced trans-abdominally (*Alvarez* and *Caldeyro* 1950 *Eskes* 1962)

Tonus and intensity (=maximal uterine pressure diminished by tonus) were expressed in mmHg, the frequency of the uterine contractions was given in the number per 10 minutes and uterine activity was expressed in Montevideo Units (*Caldeyro-Barcia et al* 1957) The maximal uterine activity—calculated over a period of 20 minutes—of these 22 patients during administration of Partocon has been compared with the maximal spontaneous uterine activity (Table I)

The indications for induction were devided as follows

1 × intra-uterine foetal death (30 weeks)
2 post-maturity with meconium-stained amniotic fluid obtained by trans-abdominal amniotic puncture (43 and 44 weeks)
4 post-maturity with an insufficient quantity of amniotic fluid (43 and 44 weeks)
4 toxaemia (39–43 weeks) of whom two also had meconium-stained amniotic fluid.
2 social indication (40 weeks)
5 ruptured membranes at term without labour (38–41 weeks) (in two of these cases there was also a toxaemia)
4 secundary uterine inertia (37–43 weeks)

Parity distribution
15 primigravidae
7 multigravidae

Age distribution
1 aged 16

van Gent, I Eskes, T and Seelen, J. C Acta obst. et gynec. scandinav 46 340, 1967
From the University Department of Obstetrics and Gynaecology St Radboud Hospital Nijmegen The Netherlands

CHANGES IN INTRA UTERINE PRESSURE DUE TO INTRANASAL ADMINISTRATION OF OXYTOCIN (PARTOCON)

BY

I VAN GENT T ESKES AND J C. SEELEN

Introduction

To induce labour intravenous infusion of dilute synthetic oxytocin is preferable both from a physiological-pharmacological and from a clinical-obstetrical point of view Nevertheless in certain cases it is possible to obtain after a slight stimulation of the uterine activity a kind of start motor effect to which the uterus responds and labour becomes effective For this purpose intramuscular injections of oxytocin can be used (at least in increments with a low initial concentration 100 200 400 800 mU) while also intranasal or buccal administrations can be applied.

For a more efficient study of intranasal administration of a new drug synthetic oxytocin (Partocon) in a relatively small group of pregnant patients mainly with pathological pregnancies in whom labour had to be induced *clinically* intra-uterine pressure was recorded. This permitted a quantitative determination of the features of uterine activity and thus an interpretation of data.

Material and Methods

Partocon is the trade name of synthetically prepared oxytocin. It was supplied by Ferring AB in 2 ml bottles of 100 I U per ml, together with a rhinyle a plastic application tube having a graduation of 0 05 0 1 and 0 2 ml corresponding to 5 10 and 20 I U

Fig. 1. Mrs. H. B. age 31 years. Sixth gravida, fourth para. Intra-uterine death caused by active rhesus antagonism. Labour induced in the 30th week with Partocon intranasally. Continuous intra-uterine pressure record shows a normal pattern. No Partocon was administered after 12.48. Six hours after the first administration a dead foetus of 1770 g was born.
C.D. = Cervical Dilatation.

Table I

	Greatest Activity Registrated in a 10 Minutes Period before Partocoon was Administered				Maximal Activity during Administration of Partocon			
	Tonus	Int.	Freq	M U	Tonus	Int.	Freq	M.U.
1 G–V	7	50	3.4	170	2	50	3.9	195
2. V–K	4	56	3 7	207	9	56	5.9	329
3. C–V	7	49	4 8	235	7	42	5.7	239
4 C–v.R					4	46	3.9	179
5 D–L					7	27	4 7	127
6. M–B	9	37	4.5	144	5	38	3.8	144
7 R–V	4	23	4.0	92	4	38	3 5	133
8. B–P					6	33	5 0	165
9 vW–H	8	36	4.8	173	8	40	5.2	208
10 H–S	5	34	3.9	133	6	39	3.3	129
11 K–D	5	46	2.5	115	9	56	3.9	218
12. N–S	6	31	4 1	127	8	30	4 8	144
13. M–N	10	42	5.3	223	14	39	5.0	195
14 V–vB	12	34	4.3	146	8	56	4.3	241
15. vD–N					3	42	2.9	122
16. vH S					5	40	6.7	263
17 K–S					3	21	4.8	103
18. vT–vO	6	32	4.2	134	5	42	3.7	155
19 X–vdB	17	57	3 5	200	16	47	3.2	150
20 P–B	8	44	2 1	92	7	29	4 8	139
21 L–D	8	32	5.6	179	4	28	5 3	127
22. V–vdH				N=15	3	34	4 7	160 N=22
Mean value	8	40	4 0	158	7	40	4.5	197
Standard deviation	3	10	0.9	45	3	10	0.9	50

Value of significance (p) spontaneous activity compared to activity during Partocon administration $0.05 > p > 0.015$

Calculations were made according to the formula given by *Dixon W J* and *Massey F J* in Introduction to Statistical Analysis ed 2, New York 1957 Mc Graw p. 303.

17 between 20 and 30 years
4 between 30 and 35 years

Intact or ruptured membranes

16 intact
6 ruptured, of whom 2 had a high rupture of the membranes.

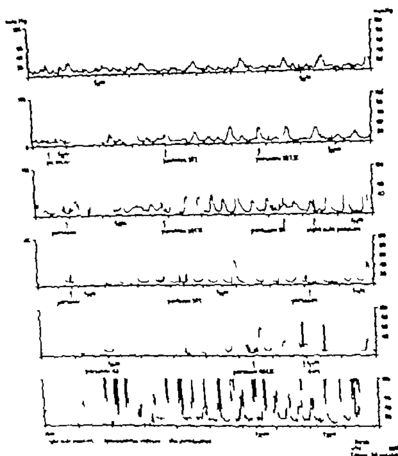


Fig 3 Mrs W H 26 years old, primigravida, had meconium stained amniotic fluid (toxaemia with hypertension) In the 39th week labour was induced Top low spontaneous activity

Intermittent and increasing doses of Partocon came an increase of uterine activity 14 08–14 58 fragment and 16.20–17 10 fragment showing good level of uterine activity 10 Montevideo Units. Below 19 39 spontaneous rupture of the membranes at complete dilatation, final stage of labour and birth (baby weight 3450 g, apgar score 10 placental weight 450 g)

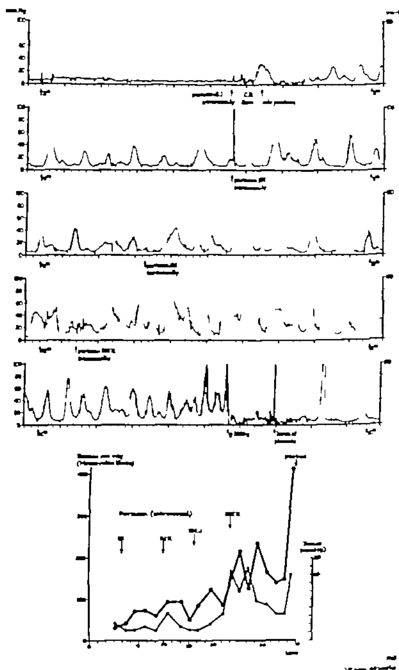


Fig 2 Mrs M–N 30 years old, seventh gravida, sixth para. Normal pregnancy Labour was induced in the 40th week. Initiation of uterine activity can be seen 4 minutes after administration of 5 I.U Partocon. The vertical lines are caused by flushing the catheter Hypertonia caused by use of 20 I.U Partocon intranasally at 10 48. The 11 40–12.30 fragment shows intra-uterine pressure during birth (baby weight 3320 g apgar score 10, placenta 450 g) The second post partum contraction is recorded with a sensitivity of 0–300 mmHg and is 200 mmHg Below graph showing uterine response in Monevideo Units and tonus (mmHg)

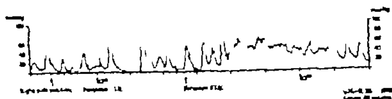


Fig. 5. Mrs. v.H. S 25 years old, had labour induced in the 43rd week of her first pregnancy for post maturity with a toxaemia and a decreasing quantity of amniotic fluid.

Four minutes after intranasal administration of 5 I.U. Partocon there was a distinct increase of uterine tonus which remained above 16 mmHg during 20 minutes (tonic hypertonus or contracture). A healthy child was delivered the next day (birth weight 2940 g, apgar score 10, placental weight 530 g).

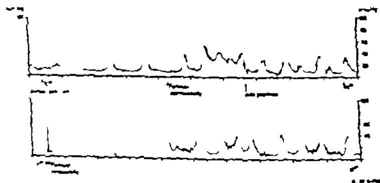


Fig. 6. Mrs. N. S 22 years old primigravida had labour induced in the 43rd week of pregnancy for post maturity with meconium stained amniotic fluid. Six minutes after administration of 5 I.U. Partocon "tetanic" hypertonus (16 mmHg) was seen. It lasted for 7 minutes and disappeared by changing the patient from the supine to the lateral position. A healthy child (weight 4160 g) was finally extracted by forceps due to a delay in the second stage of labour. Apgar score 10, placental weight 545 g.

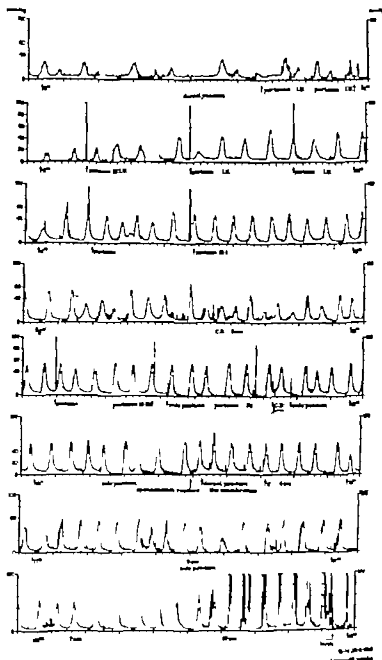


Fig 4 Intra-uterine pressure ecord of Mrs G V 22 years old, primigravida, who had a hypertension. Labour was induced in the 42nd week because of post maturity There is a good response to Partocon, showing a good level of uterine activity (190 Montevideo Units in the 14.32–15 23 strip) (baby weight 3050 g apgar score 10 placental weight 370 g)

Results

After intranasal administration of Partocon 5 to 6 minutes elapsed before an enhanced uterine activity became visible. The duration of this effect after the first dose was about 20 minutes after which in general the level of activity remained higher

The dose administered and the interval before reapplication were subject to great fluctuations and dependant on the effect observed.

With the exception of one case we invariably started with 5 I.U If the effect was only slight, 10 I.U were administered after about 15 minutes and then 20 I.U In two patients the dose was increased to 40 I.U each time. If the uterine activity was satisfactory the same dose was reapplied after 15 minutes or longer until labour progressed without further administration of oxytocin. Uterine activity was higher during administration of Partocon than spontaneous activity The value of significance (p) being between 0.05 and 0.015

Some intra-uterine pressure records will show wanted or unwanted effects of Partocon

I Mrs H S 31 year-old sixth gravida, fourth para with an active hesus antagonism, was admitted in the 30th week with an intra-uterine foetal death There was no spontaneous activity With intermittent doses of Partocon (total quantity 305 I.U.) labour was induced (Fig. 1) Six hours after the first administration the membranes were ruptured artificially dilatation being completed and dead foetus of 1770 g was born in breech presentation.

II Mrs M N 30-years-old seventh gravida, sixth para, had normal pregnancy Labour was induced for social reasons in the 40th week in Parto- on There was no spontaneous uterine activity but on administration of 5 I.U intranasal Partocon, non-painful uterine contractions were recorded (Fig) After administration of 20 I.U hypertonia by polysystolia occurred (Fig 2)

In total 45 I.U (1 × 5 I.U 2 × 10 I.U 1 × 20 I.U) of Partocon were used, and 3 hours after induction the patient was delivered of healthy daughter of 3370 grams

III In Mrs W H, 25-years-old, meconium stained amniotic fluid was found on transabdominal amniotic puncture in the 35th week of her first pregnancy (toxaemia with hypertension) Labour was induced with Partocon 305 I.U (1 5 I.U 2 × 10 I.U 2 × 30 I.U 3 × 20 I.U and 4 × 40 I.U) As can be seen in Fig 3 the pressure recorded was normal

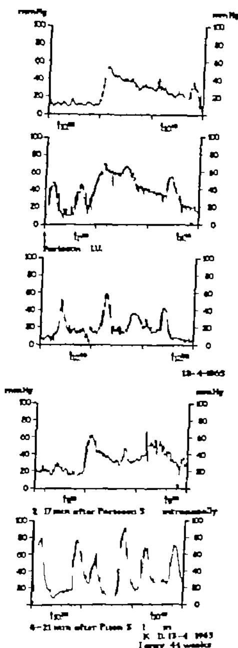


Fig. 7 Mrs K – D 25 years old primigravida. Labour was induced in the 43rd week because of post maturity with meconium stained amniotic fluid.
Top strip spontaneous tonic hypertonia in supine position. Second strip same type of hypertonia following first dose of 5 I.U Partocon intranasally
Third strip tetanic hypertonia during intravenous drip of synthetic oxytocin 3/4 mU/minute (Piton-S)
Forth strip shows same reaction to Partocon 5 I.U intranasally on the following day (top) and polysystolia after intramuscular injection of 2 I.U of synthetic oxytocin (Piton-S) (Spontaneous delivery birth weight 3210 g,

a rapid and strong increase in tonus and by the absence of rhythmic contractions
2. by a rapid increase in frequency of uterine contractions so that the uterus does not relax sufficiently between contractions (polysystolia)

Our *in vivo* observations would seem to confirm this finding for the pregnant human uterus if on reliable grounds we assume that the resting pressure must not be higher than 10 to 12 mmHg.

In the group of post-mature labour described both types of hypertonia were observed, *spontaneously* as well as on administration of oxytocin (Fig. 7) Also in serious toxaemia this possibility should be allowed for as was observed several times in our material, which comprises 120 intra-uterine pressure records.

When labour is induced the occurrence of a hypertonia may be regarded as a serious complication, because a relatively long lasting hypertonia will affect the foetus the effect being stronger according as the pregnancy is more pathological. It would therefore seem advisable in case of inductions on medical indication and hence pathology in pregnancy to ascertain whether spontaneous or induced hypertonia occurs, which is possible by means of an intra-uterine pressure record. In these cases it is possible to arrest such hypertonia at once with drugs from the catechol amine series (*e.g.* Cc 25) (*Stolte et al.* 1965)

We have found, *however that when using strongly diluted* solutions of oxytocin which permit of low initial dose anomalies are less frequent. This means

(a) for intravenous infusions a solution of 1 I U on 500 ml glucose 5 % (10 drops per minute = 1 mU/min.)

(b) for intramuscular injection an initial dose of 100 mU

Dependent on the reaction the thresholdvalue of the uterus can be found by doubling the dose at intervals of 30 and 45 minutes respectively after which the next dose being the double of the preceding one mostly causes a maximum of uterine activity From the experience with the intranasal administration of Partocon described in this group of patients, an initial dose of 5 I U in pathological pregnancy seems too high.

IV Mrs G – V 22 years old had a hypertension since the 38th week of her first pregnancy (150/100) Because of postmaturity labour was induced in 42nd week. We used 4 × 5 I.U 6 × 10 I.U 4 × 15 I.U, 1 × 20 I.U 4 × 10 I U and 1 × 20 I U (220 I U) The record of her labour (Fig. 4) was normal.

In six cases a hypertonia (> 16 mmHg) was observed following administration of 5 I U Partocon. A noteworthy feature is that in four out of the six cases post-maturity was involved, of which in two cases little amniotic fluid and two cases meconium-stained amniotic fluid was present All the six patients had been on a salt less diet during the last few weeks in connection with increased diastolic blood pressure (> 130/90) Only once did the foetal heart respond by a slower and irregular rhythm.

Twice a hypertonia occurred after a dose of 20 I.U which in these cases was therefore probably too high. One of these two was the case of Mrs M – N (Fig 2)

V Mrs. v.H – S 25 years old was in the 43rd week of her first pregnancy Labour was induced for toxaemia with post-maturity and a decreasing quantity of amniotic fluid. Seven minutes after administration of 5 I U intranasal Partocon there was a distinct increase in tonus which remained above 16 mmHg during 20 minutes (Fig. 5)

VI. Mrs. N – S 22 years old, had labour induced in the 43rd week of her first pregnancy for post-maturity with meconium-stained amniotic fluid. Spontaneous uterine activity was low Six minutes after the first dose of Partocon (5 I U intranasally) the tonus increased above 16 mmHg and remained so for seven minutes (Fig 6)

VII. An another example of hypertonia can be seen in Fig 7 which shows five fragments taken from the record of Mrs K – D 25 years old. On the 44th week of her first pregnancy labour was induced because of meconium-stained amniotic fluid. Spontaneous uterine activity showed short periods of increased tonus. After 5 I.U Partocon there was a distinct increase of the resting pressure The same is observed after intramuscular administration of 2 I.U oxytocin and during an intravenous drip-infusion of 0.75 mU./minute

Discussion

It would seem that the resting pressure in the uterus can be affected in two ways as *Jung* (1961) demonstrated *in vitro*

1 by a contracture like mechanism, which is characterised by

a rapid and strong increase in tonus and by the absence of rhythmic contractions,

2. by a rapid increase in frequency of uterine contractions so that the uterus does not relax sufficiently between contractions (polysystolia)

Our *in vivo* observations would seem to confirm this finding for the pregnant human uterus, if on reliable grounds we assume that the resting pressure must not be higher than 10 to 12 mmHg

In the group of post-mature labour described, both types of *hypertonia* were observed, *spontaneously* as well as on administration of oxytocin (Fig 7) Also in serious toxaemia this possibility should be allowed for as was observed several times in our material, which comprises 120 intra-uterine pressure records.

When labour is induced the occurrence of a hypertonia may be regarded as a serious complication, because a relatively long lasting hypertonia will affect the foetus the effect being stronger according as the pregnancy is more pathological. It would therefore seem advisable in case of inductions on medical indication and hence pathology in pregnancy to ascertain whether spontaneous or induced hypertonia occurs which is possible by means of an *intra-uterine pressure record*. *In these cases* it is possible to arrest such hypertonia at once with drugs from the catecholamine series (*e.g* Cc 25) (*Stolte et al.* 1965)

We have found, however that when using strongly diluted solutions of oxytocin, which permit of low initial dose anomalies are less frequent. This means

(a) for intravenous infusions a solution of 1 I.U on 500 ml glucose 5 % (10 drops per minute = 1 mU/min.)

(b) for intramuscular injection an initial dose of 100 mU

Dependent on the reaction the thresholdvalue of the uterus can be found by doubling the dose at intervals of 30 and 45 minutes respectively after which the next dose, being the double of the preceding one mostly causes a maximum of uterine activity From the experience with the intranasal administration of Partocon described in this group of patients, an *initial dose of* 5 *I.U* in pathological pregnancy seems too high.

IV Mrs. G – V 22 years old had a hypertension since the 38th week of her first pregnancy (150/100) Because of postmaturity labour was induced in 42nd week. We used 4 × 5 I U 6 × 10 I U 4 × 15 I.U 1 × 20 I.U 4 × 10 I.U and 1 × 20 I U (220 I U) The record of her labour (Fig. 4) was normal.

In six cases a hypertonia (> 16 mmHg) was observed following administration of 5 I U Partocon. A noteworthy feature is that in four out of the six cases post-maturity was involved, of which in two cases little amniotic fluid and two cases meconium-stained amniotic fluid was present. All the six patients had been on a salt less diet during the last few weeks in connection with increased diastolic blood pressure (> 130/90) Only once did the foetal heart respond by a slower and irregular rhythm.

Twice a hypertonia occurred after a dose of 20 I.U which in these cases was therefore probably too high. One of these two was the case of Mrs. M – N (Fig 2)

V Mrs. v.H – S 25 years old, was in the 43rd week of her first pregnancy Labour was induced for toxaemia with post maturity and a decreasing quantity of amniotic fluid. Seven minutes after administration of 5 I.U intranasal Partocon there was a distinct increase in tonus which remained above 16 mmHg during 20 minutes (Fig. 5)

VI. Mrs N – S 22 years old, had labour induced in the 43rd week of her first pregnancy for post-maturity with meconium-stained amniotic fluid. Spontaneous uterine activity was low Six minutes after the first dose of Partocon (5 I U intranasally) the tonus increased above 16 mmHg and remained so for seven minutes (Fig. 6)

VII. An another example of hypertonia can be seen in Fig 7 which shows five fragments taken from the record of Mrs K – D 25 years old. On the 44th week of her first pregnancy labour was induced because of meconium-stained amniotic fluid. Spontaneous uterine activity showed short periods of increased tonus After 5 I.U Partocon there was a distinct increase of the resting pressure. The same is observed after intramuscular administration of 2 I.U oxytocin and during an intravenous drip-infusion of 0 75 mU/minute

Discussion

It would seem that the resting pressure in the uterus can be affected in two ways as *Jung* (1961) demonstrated *in vitro*

1 by a contracture -like mechanism which is characterised by

in the human evidence was found in this study) this can be blocked by the administration of a catecholaminederivative (Stolte et al. 1965)

REFERENCES

Alvarez H. and Caldeyro R., Surg. Gynec. Obstet. 91 1, 1950

Borglin N E. Acta obst. et gynec. scandinav 41 238, 1962

Caldeyro-Barcia R. Sica-Blanco, Y., Poseiro J J Gonzales-Panizza V H Mendez-Bauer C Fielitz C., Alvarez H. Pose S.V and Hendricks C.H J Pharm. Exper Therap. 121 18, 1957

Eskes T De druk in de menselijke uterus voor tijdens en na de baring, Thesis, Nijmegen 1962

Hendricks C H. and Gabel R. A. Am. J Obst. & Gynec. 79 789 1960

Jung, H The effect of oxytocin on the mechanism of uterine excitation in oxytocin proceedings of an international symposion held in Montevideo 1959 Ed Caldeyro-Barcia, R Heller H. Pergamon Press New York 1961

Stander R. W Thompson J F and Gibbs C. P Am. J. Obst. & Gynec. 85 193, 1963

Stolte L. Eskes T Seelen J Moed H., and Vogelsang, C Am J Obst. & Gynec 79 789, 1960 1965.

Received on June 6th, 1966

A study by *Hendricks* and *Gabel* (1962) in a group of 2 normal pregnant patients intranasal administration of Synto cinon (concentration 40 I U./ml initial dose of 800 mU as spray or 500 mU as a drop) did not reveal hypertonia. Althoug in a healthy pregnancy the influence of oxytocin will probabl not so readily cause hypertonia it would seem advisable, par ticularly in pathological situations to use such strongly dilute solutions (also with Partocon) that the first dose will have n effect and only subsequent double doses will be effective, so a *to allow an individual scheme to be drawn up*

In the study of *Stander Thompson* and *Gibbs* (1963) abou 1 % of oxytocin which is applied intranasally appeared to b resorbed this comes to 50 mU in the smallest dose used in thi investigation *i e* a high dose Intranasal oxytocin can be ver easily applied by the patient herself We would like to emphasiz that in view of the risk of hypertonia it is not desirable to leav it to the patient without satisfactory supervision.

SUMMARY

In 22 pregnant patients in which labour had to be induced because of presumed postmaturity (6 ×) toxaemia *(4 ×) intra* uterine foetal death (1 ×) early spontaneous rupture of the membranes (5 ×) secondary uterine inertia (4 ×) and normal term pregnancy (2 ×) a new method of intranasal application of oxytocin (Partocon 100 I U./ml) was tested To judge all parameters of uterine activity the intra-uterine pressure was recorded. In six cases of presumed postmaturity a distinct hypertonic state was seen spontaneously (1 ×) as well as evoqued by the lowest first dose of Partocon (5 I U) (6 ×) recommended by *Borglin* (1962)

It is emphasized that if one is to induce labour in a pathological *pregnancy one has to administer a low dose of oxytocin* regardless of the method of administration there after doubling the dose till the thresholdvalue of the individual uterus is reached, the following dose *being used to obtain the maximum level of uterine* activity

If a hypertonic state is seen (either due to a stimulation of the tonic or the tetanic system *(Jung 1961)* for which existance

ing methylergometrine maleate (Methergin® Sandoz) intravenously at the time of delivery of the baby's shoulders.

C.C.T. is performed as follows. First, wait a few minutes until signs appear that the placenta is beginning to separate. The physician stands on the patient's left. Check that the uterus has contracted, and with the right hand grasp the junction of the corpus and the lower uterine segment between the thumb and forefinger and, pressing evenly, lift the uterus upwards and back. At the same time apply firm and steady traction to the forceps attached to the umbilical cord. Since the uterine cavity in the region of the lower segment may easily be constricted, once the uterus has been elevated, the right hand should be moved towards the fundus. (Fig. 1.) If the placenta is not separated in this way at the first attempt, repeat the procedure after a few minutes.

The results were treated statistically in an Elliott 503 electric data processing machine. C.C.T. was denoted by 1 and F.P.E. by 0. The statistical difference was

almost significant when	$0.027 \leq r < 0.035$
significant when	$0.036 \leq r < 0.045$
highly significant when	$r \geq 0.046$

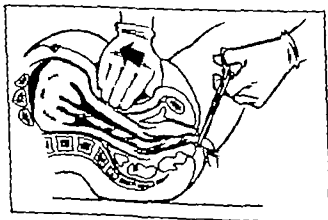


Fig. 1. Technique of controlled cord traction.

Laitinen Osmo and Jahkola, Alarik Acta obst. et gynec. scandinav. 46, 354, 1967

From the Institute of Midwifery (Professor Heikki Pitkänen) Helsinki Finland

CONTROLLED CORD TRACTION IN THE MANAGEMENT OF THE THIRD STAGE OF LABOUR

BY

OSMO LAITINEN AND ALARIK JAHKOLA

Brandt in 1933 and *Andrews* in 1940 described a technique for the management of the third stage of labour which was essentially different from the "Fundal placental expression (F.P.E.) generally employed (*Martius* 1964 *Pschyrembel,* 1958) The Brandt-Andrews technique and its modifications can be referred to collectively as "controlled cord traction (C.C.T.) In Anglo-Saxon countries it is considered to be as good as and even superior to F.P.E. (*Bonham* 1963 *Brews* 1963 *Clyne* 1963 *De Lee et al* 1948 *Donald* 1964 *Greenhill* 1954, 1965 *Hibbard* 1964 1966 *Kimbell* 1958 *Lewis* 1964 *Spencer* 1962) German teext books of obstetrics however generally fail even to mention it (*Anderer* 1952 *Bickenbach* 1962 *Burger* 1952 *Koller,* 1948 *Martius* 1962, 1964 *Naujoks* 1951 *Pschyrembel,* 1958 *Seitz Amreich* 1952 *Stoeckel* 1956)

To elucidate this point the present authors studied the subject in a series of Finnish parturients

Material and Method

The series consisted of *2760 parturients in the Institute* of Midwifery in 1963–1965 whose third stage of labour was managed by the C.C.T method The control series comprised 2255 patients delivered during the same years whose third stage of labour was managed by F.P.E. All the patients were given 0.12

was related to the significantly lower incidence of defective or torn membranes and of puerperal thromboses and other disturbances. There were no cases of shock caused by F.P.E. as described in the literature (*Brews Picton*) nor was there a single instance of inversion of the uterus in either group in this series. Two inversions occurred in other deliveries out of a total of about 10 000 during the same period. These were not included in the present material and the third stage of labour was managed by F.P.E. in both cases.

The study seems to indicate that the Anglo-Saxon view of the management of the third stage of labour is well founded.

SUMMARY

In the Institute of Midwifery in 1963-1965, the third stage of labour of 2760 parturients was managed by controlled cord traction and the third stage of labour of 2255 control patients was managed by the fundal placental expression method.

The parturients managed by controlled cord traction showed

- a lower incidence of retained placenta the difference was statistically highly significant
- a lower incidence of manual removal of the placenta the difference was statistically highly significant
- a lower incidence of defective or torn membranes the difference was statistically significant
- fewer thromboses and other puerperal complications the difference was statistically almost significant
- a shorter stay in hospital post partum the difference was statistically highly significant.

No statistical difference in bleeding was demonstrated between the two methods.

There was no case of inversion or the uterus in either group

Acknowledgement

This investigation was aided by the grant from the Mater Foundation.

Table I. *Correlation Coefficients Between the Controlled Cord Traction and Fu... Placental Expression Methods*

Hemorrhage	Expulsion of secundines	Manual removal of placenta	Torn placenta	Defective membranes	Curettage etc.	Contraction of uterus	Puerperal infection	Puerperal thrombosis	Other puerperal disorders	Hospital stay
−0 018	0.057	−0 064	−0 009	−0 041	−0 002	−0 024	−0.008	−0.032	−0 030	0 06

Results

The correlation coefficients between C C.T and F.P.E. are shown in Table I

Retention of the placenta was less common with C.C.T (r = 0 057 highly significant) and manual removal was less frequently required (r = 0 064 highly significant) The membranes were less frequently defective or torn with C C T (r = 0.041 significant) The incidence of puerperal thromboses and other complications was lower in this group (r = 0 032 and 0 030 respectively almost significant) The hospital stay *post partum* was shorter for C C T patients (r = 0 065 highly significant)

There was no case of uterine inversion in either group.

Discussion

Comparison of C C T and F P E showed that the secundines are more often expelled primarily with C C T and that the difference from F.P.E. is statistically highly significant. The incidence of *post partum* bleeding has been reported to be smaller with C.C T than with F P E (*Bonham Clyne Fliegner* and *Hibbard Kimbell Picton Spencer*) but it was not possible to demonstrate any statistical difference in the present series. On the other hand, manual removal of the placenta after F.P.E. was necessary much more frequently and the difference was statistically highly significant Similar results have been obtained by e g *Brews* (1963) *Dutton* (1958) *Elwin* (1960) *Fraser et al* (1961) *Kimbell* (1958) *Picton* (1951) The hospital stay *post partum* was significantly shorter for the C C.T patients. This

Jäykkä, S. and Laakso, L., Acta obst. et gynec. scandinav. 46, [illegible], 1967
From the Department of Obstetrics and Gynaecology (Prof. Lauri Rauramo) the University of Turku and from the Lying-in Hospital (Matti Takala M.D.) the City of Turku, Finland

CHANGES IN SKIN TEMPERATURE DURING THE FIRST MINUTE OF LIFE AS SIGNS OF CIRCULATORY TRANSITION AT BIRTH

BY

S. JÄYKKÄ AND L. LAAKSO

Introduction

It has long been customary to assess the condition of a newborn child from the skin colour. The change in the colour of the skin of the newborn to pink is evidently a consequence of blood perfusion in the superficial layers of the skin. This is indicated by the observation that the colour change occurs over successive skin areas. *Jäykkä* (1961, 1964) as a result of pathoanatomical studies concluded that the afferent arterioles in the foetal lungs, kidneys, intestine and liver are in a constricted state, that poor arterial perfusion prevails in these organs during intrauterine life and that the arterioles become patent when the organs begin to function. This transition has been quite well documented as far as the lungs are concerned and it is resonable to assume that similar changes are found widely throughout the infant. Perfusion of the skin may thus be taken to represent one aspect of the general transition at the arterial level. If this perfusion actually increases when the skin of a newborn changes its colour to pink, variations should also occur in the skin temperature and it should be possible to record these. *Saling's* (1966) new concept of the preservation of oxygen by circulatory constriction in various organs is apparently one aspect of this same problem (HO_2 Sparschaltung).

REFERENCES

Anderer E. Lehrbuch der Geburtshilflichen Operationen, Verlag von S. Karger in *Basel 1952*
Andrews C J J South. Med. Surg. *67* 605 1940
Bickenbach W Hebammenlehrbuch, Georg Thieme Stuttgart 1962
Bonham D G Brit. med. J *2* 1620 1963
Brandt M L Amer J Obstet. Gynec. *25* 662, 1933
Breus A. In Holland & Brews Manual of Obstetrics, J & A. Churchill Ltd, London 1963 pp. 334 511
Burger K. Geburtshilfliche Operationslehre Springer Verlag, Berlin-Göttingen-Heidelberg 1952
Clyne D G W A Textbook of Gynecology and Obstetrics, Longmans, London 1963, pp. 572, 701
De Lee J B. and *Greenhill J P* Principles and Practice of Obstetrics, W B Saunders Company Philadelphia and London 1948, p. 273
Donald I Practical Obstetric Problems, Lloyd-Luke (Medical Books) Ltd, London 1964 p 569
Dutton W A. C. J Obstet. Gynaec. Brit. Emp. *65* 315 1958
Elwin P M Brit. med. J *1* 1569 1960
Fliegner J R. and *Hibbard B. M* Brit. med. J *2* 622, 1966
Fraser A. C and *Tatford E. P W* Lancet *2* 126 1961
Greenhill J P Year Book of Obstetrics & Gynecology 1953–1954, Year Book Medical Publishers, Chicago 1954 p 213
– Year Book of Obstetrics & Gynecology 1964–1965 Year Book Medical Publishers, Chicago 1965 p. 216
Hibbard B M Brit. med J *1* 1485 1964
Kimbell N Brit. med. J *1* 203, 1958
Koller Th. Lehrbuch der Geburtshilfe Verlag von S Karger in Basel 1948
Lewis T L T Progress in Clinical Obstetrics and Gynecology J. & A. Churchill Ltd, London 1964 p. 51
Martius H Die geburtshilflichen Operationen, Georg Thieme Verlag, Stuttgart *1962*
– Lehrbuch der Geburtshilfe, Georg Thieme Verlag, Stuttgart, 1964
Naujoks H In Winter-Naujoks, Lehrbuch der operativen Geburtshilfe Urban & Schwarzenberg, München-Berlin 1951
Picton F C. R., J Obstet. Gynaec. Brit Emp *58* 764 1951
Pschyrembel W Praktische Geburtshilfe Walter de Gruyter & Co, Berlin *1958*
Seitz Amreich Biologie und Pathologie des Weibes, Verlag Urban & Schwarzenberg, München, Wien 1952
Spencer P M Brit. med. J *1* 1728, 1962
Stoeckel W Lehrbuch der Geburtshilfe Gustav Fischer Verlag, Jena 1956

Received on Sept. *27 1966*



Fig 2 Oblique skin section. The subpapillary arterial net is enclosed by rectangle Note the subpapillary arterial net, coarse enous and superficial capillary network.

were made as soon as possible after delivery then three times during the first ten minutes and at irregular intervals subsequently The temperatures were then plotted against time (Fig 1)

Results

Anatomical Observations

Three different functional systems can be distinguished in the blood circulation of the skin. An oblique section through the skin reveals the relative topography of these three blood vessel systems (Fig 2) When the microscope is focused on the innermost layer

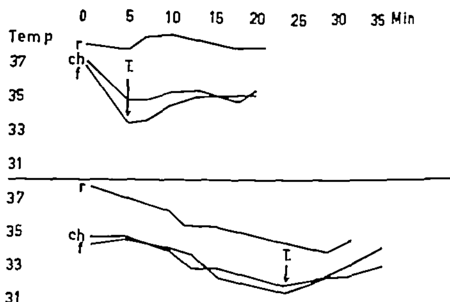


Fig. 1 Upper curves. Normal temperature variations. The moment T about 5 min. after delivery Apgar score 9. – Lower curves. Delayed temperature reversal about 25 min. after delivery Maternal toxaemia. Apgar score 9 r=rectum ch=chest, f=forehead.

Material and Methods

Three legal abortion foetuses were examined to determine the blood vessel system of the skin Indian ink was injected into the umbilical vein of each foetus while it was still alive and the foetus was then immersed in formalin The perfusion pattern of the skin was then examined directly in an unsectioned preparation. This was facilitated by the translucency of the skin. In this way for a study of perfusion a better general picture of the circulatory system was obtained than would have been possible from serial skin sections

The skin temperatures were measured with a Thermistometer manufactured by Labko Lahti Finland. The reliability of the meter was checked against a mercury thermometer by *Ennevaara* and *Isohanni* (1963) The meter rapidly and reliably responds to changes in skin temperature Measurements of temperature were made on the forehead chest and rectum. The first measurements



Fig. 4 High power magnification of the network seen in Fig. 3.

work and the middle venous net functional systems. The supply function of the subpapillary arterioles becomes more evident when the walls of the arterioles are examined with greater magnification. The bore of the arterioles is seen to be constricted by turgid muscle cells (Fig. 6).

It thus seems that the skin colour may be determined by the patency of subpapillary arterioles. When these admit well-oxygenated blood to the capillary network, the skin is pink. On the other hand lividity of the skin is probably due to congestion of the venous net and pallor to the constriction of the arterioles. No patent arteriovenous anastomoses were detected with certainty in any of the preparations.

Skin temperatures

As one of the aims of the study was to find out whether the moment when the skin temperature begins to rise is of prognostic value in the assessment of a newborn child's condition, newborns were divided into three groups according to the time that elapsed

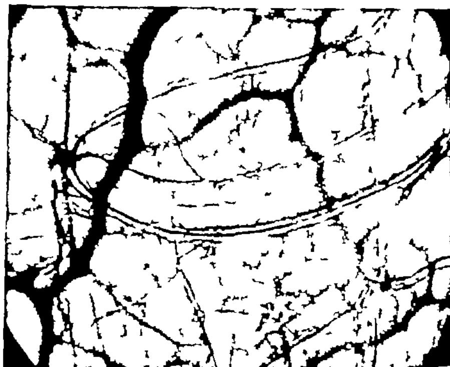


Fig. 3. A skin preparation. The microscope was focused on the deepest layer Note the "three-vessel net consisting of an arteriole in the middle and two concomitant veins The coarse venous net between the superficial capillary net and subpapillary arterial net is seen indistinctly outside the focal plane.

of the skin membrane the first functional circulatory network is seen, which consists of loops formed by three parallel blood vessels, of which the middle one is an arteriole and the other two concomitant venules. This network is only rarely depicted in textbooks on anatomy although it is particularly well discerned in the skin of the foetus (Figs. 3 and 4)

This subpapillary arterial network supplies blood to a superficial capillary network and it is the latter which determines the colour of the skin (Fig 5)

After passing through the superficial capillary network the blood enters a coarse venous net, which is the third functional system The blood finally flows into the concomitant veins of the subpapillary network Anatomically the subpapillary arterial network is the supply system and both the superficial capillary net

Table I. Group I *The Time that Elapsed from Delivery to the Moment 1 T < 5 Min.*

Birth Weight	Duration of Delivery		Amniotic Fluid		Apgar Score	Complications
	Hours	Min	Clear	Dis-coloured		
650 g			+		9	
800	7	00	+		8	
740	12	50	+		8	
1780	20	50	+		10	
1200	14	55	+		9	
1270	12	05		+	10	
1350	1	45	+		10	

7 cases

Table II. Group II *The Time that Elapsed from Delivery to the Moment T was 5–10 Min.*

Birth Weight	Duration of Delivery		Amniotic Fluid		Apgar Score	Complications
	Hours	Min.	Clear	Dis-coloured		
3350 g	12	56	+		10	
2850	7	55	+		8	
3430	4	20	+		10	
3300	15	50	+		9	
4100	3	45	+		10	
2710	22	50	+		9	
3050	15	40	+		9	
3350	9	50	+		9	
4150	5	25	+		9	
3550	17	50	+		8	
400	5	25	+		9	
3000	16	20	+		10	
3150	6	20	+		9	
3350	11	48	+		10	
4000	8	38	+		9	
3200	14	40	+		9	
4300	7	05	+		9	
3200	15	05	+		7	
3550	13	55	+		10	

19 cases

Fig. 5 Capillary network in sharp focus at the surface of the skin preparation.

Fig 6. Arteriole of the network seen in Fig 4 Muscle cells are indicated by

Table I. *Group I The Time that Elapsed from Delivery t the Moment ΔT < 5 Min.*

Birth Weight	Duration of Delivery		Amniotic Fluid		Apgar Score	Complications
	Hours	Min.	Clear	Dis-coloured		
3650 g			+		9	
2800	7	00	+		8	
3740	12	50	+		8	
3780	20	50	+		10	
3200	14	55	+		9	
4270	12	05		+	10	
3350	1	45	+		10	

7 cases

Table II. Group II The Time that Elapsed from Delivery to the Moment T was 5–10 [illegible]

Birth Weight	Duration of Delivery		Amniotic Fluid		Apgar Score	Complications
	Hours	Min	Clear	Dis-coloured		
2250 g	12	56	+		10	
2850	7	55	+		8	
3430	4	20	+		10	
3700	15	50	+		9	
4100	3	45	+		10	
2710	22	50	+		9	
3050	15	40	+		9	
3350	9	50	+		9	
4150	5	25	+		9	
3550	17	50	+		8	
2400	5	25	+		9	
3000	16	20	+		10	
3150	6	20	+		9	
3350	11	48	+		10	
4000	8	38	+		9	
3200	14	40	+		9	
4300	7	05	+		9	
3200	15	05	+			
3550	13	55	+		10	

19 cases

Fig. 5 Capillary network in sharp focus at the surface of the skin preparation.

Fig. 6. Arteriole of the network seen in Fig. 4 Muscle cells are indicated by arrows.

between delivery and the moment when the lowest skin temperature was recorded (Fig. 1 T)

In the first group (Table I.) the temperature rose within 5 minutes, in the second group (Table II.) within ten minutes and in the third group (Table III.) after ten minutes had elapsed. Other important prognostic criteria were the birth weight, the duration of labour the quality of the amniotic fluid, the Apgar score and other complications noted during pregnancy and delivery

Discussion

The skin temperature of a normal newborn infant undergoes a typical uniform change during the early minutes after delivery There is a fall in the temperature-time curve, which normally appears within 5 to 10 minutes after delivery Groups I and II were free of complications and also had high Apgar scores indicating a vigorous response. It hence seems justified to conclude that a skin temperature decrease that occurs within ten minutes after delivery is a normal reaction. The level to which the temperature falls seems to be of no significance. Temperatures measured on the forehead and chest vary similarly The variations of the rectal temperature were not as uniform and did not follow the variations of the skin temperatures, since the rectal temperature in some cases increased up to 39 C while skin temperature decreased. The rectal temperature sometimes was still falling when the skin temperature had already passed its nadir

Group III was characterized by a large number of complications. All the newborn infants with low Apgar scores (less than 7 points) fell in this group In four cases the Apgar scores were normal, but the temperature reversal was delayed. Also in these the course of pregnancy or delivery revealed an acceptable reason for the delayed reaction (maternal toxaemia discoloured amniotic fluid) Only three cases gave a false alarm when ten minutes was taken as the limit between normal and delayed temperature reaction Thus apart from other unfavourable reactions of asphyxiated foetuses, the delayed skin temperature change seems to be of considerable prognostic value when the condition of the newborn is assessed.

Table III. *Group III The Time that Elapsed from Delivery to the Moment T> 10 Mi*

Birth Weight	Duration of Delivery		Amniotic Fluid		Apgar Score	Complications
	Hours	Min.	Clear	Dis-coloured		
3650 g	15	11		+	9	Maternal toxaemia
2700	15	30		+	8	
3050	9	45		+	10	
3550	34	40		+	9	Maternal toxaemia
3550	6	55	+		4	Calcified placenta Breech presentation Erbs palsy
2850	22	25	+		7	Calcified placenta
2800	5	05	+		6	Gemini B. Breech presentation
3300	21	20	+		7	Respiratory distress
3600	13	25	+		7	Calcified placenta
3500	19	20	+		10	Maternal toxaemia Vacuo extract.
3300	21	30	+		7	
2250	12	25	+		8	Gemini A. Feet presentation
2450	12	35	+		10	Gemini B
3500	19	20	+		9	Maternal toxaemia Vacuo extract.
3300	21	30	+		7	Asphyxia
3400	4	48	?		5	Placenta previa
2850	13	30	+		10	
4550	18	56	+		9	
2850	22	25	+		7	Calcified placenta
2800	5	05	+		6	Gemini B Breech presentation
3300	21	20	+		7	Respiratory distress
3600	13	25	+		7	Calcified placenta
3500	19	20	+		10	Maternal toxaemia Vacuo extract.
3300	21	30	+		7	
2250	12	25	+		8	Gemini A Feet presentation
?450	12	35	+		10	Gemini B
3500	19	20	+		9	Maternal toxaemia Vacuo extract.
3300	21	30	+		7	Asphyxia
3400	4	48	?		5	Placenta previa

29 cases

Kluge Trond, Skyberg, Dag, and Bjøro, Knut, Acta obst. et gynec. scandinav. 46, 388, 1967

From the Institute of Pathological Anatomy (Professor O. Torgersen), the Department of Pediatrics (Professor L. Salomonsen) and the Department of Obstetrics and Gynaecology (Professor E. Schjøtt Rivers), University of Oslo, Norway

FATAL HERPES SIMPLEX INFECTION IN THE NEWBORN

Caesarean Section as a Prophylactic Measure

BY

TROND KLUGE, DAG SKYBERG AND KNUT BJØRO

Herpes simplex infection is usually benign. In newborn infants, however, infection with this type of virus may become severe and disseminated, with a fatal outcome.

By a coincidence we observed herpes simplex infection in two newborn infants autopsied at the same time. In case no. 1 the diagnosis was confirmed prior to death, but the child died despite all therapeutic efforts.

Emphasis must be placed upon prophylaxis, as the present therapeutic measures in the newborn may be considered ineffecti e

Case reports

1. *Mother.* In 1962 she had a miscarriage in the 3rd month of pregnancy. On Jan. 19th, 1963, at the age of 21, she was admitted in premature labour with vaginal bleeding. At the time of delivery she had circumoral herpes simplex lesion. No lesions were observed in the vulva, vagina or cervix.

Infant. A premature girl, (weight 2280 g, length 44 cm) showed no abnormality until the 4th day, when she became drowsy and started vomiting. The respiration became shallow with episodes of cyanosis. Rales and crepitations were noted on auscultation. Serum bilirubin on the 5th day was 18.2 mg/100 ml. No evidence of Rh-incompatibility was found. Electrolytes were normal. White cell count was 10,600 cu mm with shift to the left. Chest X-ray was normal. Treatment with Penicillin G and Aureomycin

We propose the following interpretation of the results. As long as the foetus is in the intrauterine environment at constant temperature no temperature regulation is necessary and the skin is a dormant organ with suppressed blood circulation. When the foetus is delivered the system determining skin temperature begins to function but this requires several minutes to adapt and this time the skin temperature falls When the arteries are activated and perfusion increases a change in skin colour and rise in temperature occur

SUMMARY

It is proposed that the change in the colour of the skin to pink in a newborn infant is due to increased blood permeation which becomes evident as a rise in skin temperature of measurable degree Anatomical observations reveal that the local perfusion of the skin is dependent on the tone of arterioles of the subpapillary arterial network. Skin temperature measurements showed that a newborn infant reacts typically with an initial decrease in skin temperature which is followed by a temperature rise The change-over seems to occur normally within ten minutes after delivery When complications occur before and during delivery the temperature reversal is delayed.

Acknowledgements

The first author wishes to express his gratitude to the Medical Society Duodecim for grants in aid.

REFERENCES

Ennevaara K. and *Isohanni A* Suomen Lääkärilehti *18* 1983 1963

Jäykkä S P O Biol. Neonat. *3* 343 1961

– Ann. Paediat. Fenn. *10* 113 1964

– Biol. Neonat. 7 313 1964

Saling E. Das Kind im Bereich der Geburtshilfe p 152. Thieme Verlag, Stuttgart, 1966

Received on June 23rd, 1966



Fig 1 Centrolobular necrotic area in liver parenchyma. Case 1 Hematoxylin-eosin ×100

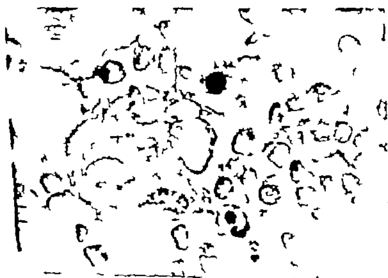


Fig 2 Fresh intranuclear inclusion body in liver cell. Note the marginal arrangement of nuclear chromatine. Case 2. Hematoxylin-eosin ×1000.

was started, but as herpes simplex viraemia was suspected, therapy was supplemented with gamma globulin (1 ml/day) and N.N-biguanide chloride (Flumidin)

Repeated white cell count was 6800 per cu mm, with a relative lymphocytosis Throat swab cultures on amniotic cell media grew large amounts of herpes simplex virus (Dr L. Flugsrud, Statens Institutt for Folkehelse, Oslo) Despite all efforts the infant's condition rapidly deteriorated with attacks of apnoea, cyanosis and vomiting, and she died on the 18th day

Autopsy RHO 0 058/65

Lungs There were irregular areas of atelectasis and congestion. The interstitial tissue was oedematous with a slight infiltration of mononuclear cells. The alveoli contained exudate with numerous macrophages. The picture was that of an interstitial pneumonia, possibly of viral origin.

Oesophagus The distal 1/3 presented a swelling of the mucosa, and microscopy revealed a small ulcer with fibrinous exudate, desquamation of epithelium and cellular infiltration.

Liver Weight normal. The parenchyma contained numerous *scattered* pinpoint-sized, yellowish areas These showed necroses, partly confluent, but mainly centrilobular (Fig. 1) The margins of these areas showed parenchymal cells with degenerative changes. Several of these contained inclusion bodies of Cowdry's type A (Fig. 2)

Adrenals The cortex showed irregular necroses, hyperaemia and extravasations of blood (Fig. 3) The margins of the necrotic areas again showed *the characteristic inclusion bodies (Fig. 4)*

Brain Slight oedema and reactive changes of the glia and small vessels, were present, possibly consistent with a low-grade encephalitis. No inclusion bodies were seen.

Final diagnosis Herpes simplex infection, generalized, with hepato-adrenal necrosis. *Interstitial pneumonia. Localized, superficial oesophagitis* with ulceration.

II. *Mother* Gravida 1 age 22. During the whole pregnancy she suffered from nausea and vomiting. Slight vaginal bleeding occurred during the last 4 months of pregnancy On Dec. 22nd, 1964 she was admitted because of cervical incompetence which was treated by cerclage. On Jan. 22nd, two weeks prior to term, she was readmitted with ruptured membranes. 48 *hours* later spontaneous delivery took place. The patient had no signs of infection during pregnancy Neither was there any evidence of herpes infection in her immediate contacts, but at the time of her admission in December some cases of pleurodynia were treated in the outpatient department, and influenza was rather common at the time. Hence, it is not *impossible that her threatened* abortion might have been a manifestation of virus infection.

Infant Male weight 3110 g, length 50 cm. From the 3rd day the child



Fig. 1 Centrolobular necrotic area in liver parenchyma. Case 1. Hematoxylin-eosin ×100

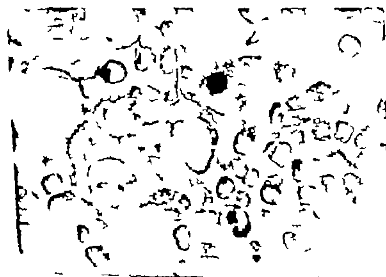


Fig. 2 Fresh intranuclear inclusion body in liver cell. Note the marginal arrangement of nuclear chromatine. Case 2. Hematoxylin-eosin ×1000.



Fig. 3 Irregular necrosis and haemorrhage in cortex and medulla of suprarenal gland. Case 2. Hematoxylin-eosin ×40



Fig. 4. Older intranuclear inclusion bodies in cortical cells of the suprarenal gland. The bodies are centrally located, faintly eosinophilic and surrounded by a clear zone, while the chromatin is peripherally located in the nuclei. Case 1 Feulgen DNA-staining ×1000

seemed lethargic and developed jaundice but was taken home despite paediatric advice. On the 13th day the weight was only 2740 g, and respiration was periodically stressed. During feed the infant became cyanotic and was re-admitted with respiratory distress. The temperature was subnormal, chest X-ray negative and white cell count was normal. On the 16th day of life, the infant condition deteriorated, and traces of blood and mucus were observed in the stools. The following day a sudden respiratory collapse occurred, and death supervened in 1 1/2 hour

Autopsy RHO 0.060/65

Lungs. Irregular areas of atelectasis and congestion. No evidence of virus infection.

Oesophagus / cardia / stomach / intestines. normal.

Liver and adrenals. The appearances were identical with those in Case 1 Characteristic inclusion bodies were detected in both organs.

Brain. Slight reactive changes in glia and capillaries.

Final diagnosis. Herpes simplex infection, generalized, with hepato-adrenal necrosis Pulmonary congestion and atelectasis.

Discussion

a) *Pathogenesis*

Maternal herpes virus disease has been demonstrated in about 1/3 of all cases described. Of particular interest are herpes lesions of the vulva, vagina and cervix (*White* 1963 *Wheeler et al.* 1965) as direct inoculation of the infant with herpes from the birth canal is believed to be the most common route of infection (*Yen* et al. 1965)

It is important to recognize that herpetic lesions on mucous membranes usually are not vesicular but appear as erosions with surrounding oedema. The herpetic cervix is dark gray oedemat ous and friable, and may resemble an infected tumour The condition seems self-healing in 6–8 weeks

Transplacental virus infection has never been proved, but is strongly suspected (*Zuelzer et al.* 1952 *Witzleben et al.* 1965) In general, any herpes manifestation in the mother prior to delivery must be considered a hazard to the infant. Other sources of infection are virus carriers among nursing personnel, patients and relatives.

b) *Clinical picture*

The incubation period of herpes virus is 1–12 days (*Witzleben et al* 1965), but most infants develop signs of disease during the first week. These include respiratory distress, lethargy hepatosplenomegaly jaundice haemorrhagic diathesis skin eruptions convulsions and circulatory collapse Premature infants are particularly prone to fatal infections (*vide infra*)

The clinical picture seems to vary with the portal of entry (*Bird et al* 1963) It is suggested that virus transmission through placenta and the umbilical cord results in the main attack falling on the liver and abdominal viscera, while oral infections produce lesions of the oesophagus and intestines. Infection through the respiratory tract mainly involves the lungs with development of a necrotizing pneumonia (*Bird et al* 1963 *Platt* 1964) However any manifestation of herpes can probably give rise to a fatal septic viraemia (*McCallum* 1957)

c) *Diagnosis*

Cytomegalic inclusion disease salivary gland virus and Coxsackie-B-infection can produce a similar clinical picture The condition also may be confused with erythroblastosis listerosis, toxoplasmosis generalized chickenpox, and perhaps most often with bacterial septicaemia

d) *Morbid anatomy*

A variety of organs may be affected most frequent are changes in the liver adrenals lung, mouth, oesophagus intestines and brain. Lesions also have been demonstrated in the spleen, lymph nodes bone marrow conjunctiva larynx, stomach and heart. Microscopically the hepato-adrenal necrosis is considered pathognomonic (*Szögi et al* 1966) The liver and adrenal cortex display irregular areas of necrosis and degeneration, with absence of the usual inflammatory changes (*Hass* 1961) The surrounding tissue contains intranuclear inclusion bodies. These vary with age but are always large, centrally located and surrounded by a clear zone The chromatin is dislocated at the periphery of the nucleus (*Cowdry* 1934) In the respiratory and gastrointestinal tract, the lesions appear as ulcers with a necrotic

center while the lungs present a pneumonitis or necrotizing pneumonia (*Wheeler et al.* 1965) Changes in the syncytiotrophoblast are described by *Witzleben et al.* (1965) who recommend a thorough examination for villous necrosis of the placenta.

e) *Virus studies*

Herpes simplex virus has been isolated from mothers infants and from autopsy specimens. An increase of serum antibodies takes place 4–7 days after the onset of infection, reaches a maximum during the 2nd–3rd week, and this level is maintained for 3–4 weeks. After this period, the titre begins to decline (*Buddingh et al* 1953 *White* 1963) In newborn infants, the increase in antibody titre can be expected from the 2nd or 3rd week.

Antibodies have been detected in 60–96 per cent of the population in western countries. It is doubtful, however whether a person once infected remains latently infected with a persistent high level of antibodies. Several cases of herpes virus disease have been reported, with an apparent absence of maternal and foetal antibodies (*Buddingh et al.* 1953 *McCallum* 1957)

Even in cases with a high titre of maternal antibodies fatal infections in the infant may occur Thus the protection from maternal antibodies is far from complete. A qualitative defect in the antibodies or an overwhelming dose of virus was postulated by *McCallum* (1957) Furthermore, *Wheeler et al.* (1965) have suggested that the transmission of antibodies may be impaired, or the route of infection such that antibodies are ineffective.

Fatal herpes simplex infection is more frequent in premature infants It is commonly known that foetal tissues are highly susceptible to virus Furthermore the main placental transfer of antibodies takes place during the last few weeks of gestation. Thus the premature infants have not received their full complement of maternal antibodies (*Buddingh et al* 1953) As the capacity of antibody formation is also less in a premature infant, both the active and the passive immunity are reduced.

f) *Treatment*

Attempts have been made to increase passive immunity in the

b) *Clinical picture*

The incubation period of herpes virus is 1–12 days (*Witzleben et al* 1965) but most infants develop signs of disease during the first week These include respiratory distress, lethargy hepatosplenomegaly jaundice haemorrhagic diathesis skin eruptions convulsions and circulatory collapse Premature infants are particularly prone to fatal infections *(vide infra)*

The clinical picture seems to vary with the portal of entry (*Bird et al*, 1963) It is suggested that virus transmission through placenta and the umbilical cord results in the main attack falling on the liver and abdominal viscera while oral infections produce lesions of the oesophagus and intestines. Infection through the respiratory tract mainly involves the lungs with development of a necrotizing pneumonia (*Bird et al* 1963 *Platt*, 1964) However any manifestation of herpes can probably give rise to a fatal septic viraemia (*McCallum* 1957)

c) *Diagnosis*

Cytomegalic inclusion disease salivary gland virus and Coxsackie-B-infection can produce a similar clinical picture. The condition also may be confused with erythroblastosis, listerosis, toxoplasmosis generalized chickenpox, and perhaps most often with bacterial septicaemia.

d) *Morbid anatomy*

A variety of organs may be affected most frequent are changes in the liver adrenals, lung, mouth, oesophagus intestines and brain. Lesions also have been demonstrated in the spleen, lymph nodes bone marrow conjunctiva, larynx stomach and heart. Microscopically the hepato-adrenal necrosis is considered pathognomonic (*S ögl et al* 1966) The liver and adrenal cortex display irregular areas of necrosis and degeneration with absence of the usual inflammatory changes (*Hass* 1961) The surrounding tissue contains intranuclear inclusion bodies These vary with age but are always large, centrally located and surrounded by a clear zone The chromatin is dislocated at the periphery of the nucleus (*Cowdry* 1934) In the respiratory and gastrointestinal tract, the lesions appear as ulcers with a necrotic

shortly after birth. Autopsy findings were typical in both cases, with hepato-adrenal necrosis and characteristic intranuclear inclusion bodies.

Results of therapy are very poor and stress must be put on prophylaxis. A careful history and examination for herpes simplex infection during the last weeks of pregnancy is emphasized. If signs of herpes infection are present, delivery by Caesarean section should seriously be considered. This applies especially if the herpetic lesions are located in the birth canal and external genitals.

REFERENCES

Bird T and *Gardner P S* J Clin. Path. *16* 423, 1963
Buddingh G. J Schrum D I Lesler J C, and Guedry D J Pediatrics, 11 595 1953
Cowdry E. V Arch Path. 13 527 1934
Hass G Amer J. Path 71 538, 1961
McCallum F O Acta Virol. Suppl. 3 17 1959
Nigogosyan, G and Mills J W J Amer med. ass *191* 496 1965
Platt H Brit. J Exp. Path. 45 300 1964
Solberg, L A Skyberg, D and *Ulstrup* J C T den norske Laegeforening, *19* 1453, 1963
Stiegs, S and Berge T Acta Path. Microbiol. Scand. *66* 401 1966
Wheeler C L, and *Huffines* W D J Amer med ass *191* 455, 1965
White J G New Engl. J Med 269 455 1963
Witzleben C L and *Driscoll* S. G Pediatrics 36 192, 1965
Wright H T J and Miller A, J Pediat 67 130 1965
Yen S S C *Reagan* J W and *Rosenthal* M. S Obstet. Gynec. 25 479, 1965
Zuelzer W and *Stulberg*, C S Am J. Dis. Child 83 421 1952

Received on Sept 14th, 1966

infant In a case reported by *Wheeler et al* (1965) a complete exchange transfusion was carried out The donor had recurrent herpes with a high titre of antibodies but the treatment did not alter the fatal course of the disease.

Injections of gamma globulin (serum immune globulin) have been tried on several occasions (*Zuelzer et al* 1952, and others) apparently without effect. In one of the rare cases where infection of the infant was expected, gamma globulin was given to the mother before and after delivery and to the infant immediately after birth (*Wheeler et al* 1965) However a significant increase of the titre did not occur until 48 hours had passed, and this is probably too late Hence, it appears that the infection very rapidly becomes so overwhelming that gamma globulin is unable to control it, even when given at the earliest time possible.

g) *Prophylaxis*

At present therapy must be considered ineffective. Prophylaxis therefore becomes the more important. This can be outlined as follows

1 If signs of herpes virus infection are present in the weeks *prior to delivery this should probably be effected* by Caesarean section, this being the only way to obtain sterile conditions. If the herpetic lesions are located in the birth canal and external genitals Caesarean section is considered mandatory

2 Isolation of newborn infants from all known sources of environmental herpes.

3 Notification and control of herpes manifestations in all personnel on the ward

4 In suspected cases injections of gamma globulin or hyperimmune globulin are recommended. The doses suggested are large e g 250 mg/kg body weight during the first 3 days (*McCallum* 1959) and 10 ml/day for 10 days to the mother (*Wheeler et al* 1965)

SUMMARY

Two cases of fatal herpes simplex virus infection in newborn infants are described. One case was diagnosed and virus cultured

minority of defects has a major environmental cause *e.g.* viruses. In the remaining cases the malformation is probably the result of an interplay between genetic predispositions and exogenous influences (Neel 1961)

Further elucidation of the importance of environmental factors in the aetiology of congenital malformations in man can be obtained only by thorough study of large series and by close co-operation between obstetricians, paediatricians, pathologists, geneticists and statisticians.

Planning of the Investigation

This prospective investigation includes all pregnant women seen at the Prenatal Care Centres in Gothenburg during the period 1954–1958 The patients at these centres come from a uniform cross section of all classes from the economic and social point of view

The planning of the investigation has earlier been described in detail in a preliminary report (*Hedberg et al.* 1963) In summary every woman was interviewed at her first visit to the Centre paying particular attention to malformations in her or her relatives as well as in the father and his relatives. Any significant disease prior to pregnancy and the outcome of previous pregnancies were noted on a standard form. This special card was completed at each visit to the Centre and notes were made concerning accidents diseases and exposure to contagious diseases during the present pregnancy As Gothenburg is unified in respect to medical attendance it has generally been easy to follow the mothers to delivery Departures from the city are few either during and after pregnancy This too facilitated collection of information about the children from the Children's Welfare Centres.

The information obtained has been coded for automatic data processing. Negative as well as positive information has been recorded and for each patient a total of about 280 different items has been listed. In the statistical analysis of the differences obtained the χ^2-test was employed.

Hedberg, E Holmdahl, K and Pehrson, S Acta obst. et gynec. scandinav 46, 378, 1967

From the Department of Obstetrics and Gynaecology (Prof S. Brody) University of Gothenburg, and the Department of Paediatrics (K. Holmdahl, M D) Uddevalla Sweden

ON RELATIONSHIP BETWEEN MATERNAL HEALTH AND CONGENITAL MALFORMATIONS

BY

E. HEDBERG, K. HOLMDAHL AND S. PEHRSON

Congenital malformations are of great importance in relation to the viability of the foetus and newborn child and to the future prognosis of the infant. The overall incidence of fairly serious malformations for all infants born after the twenty-eighth week of pregnancy and with an observation period of one year after birth is about 4–5 per cent. Taking into account that many malformations do not become manifest until childhood or adolescence, no doubt the true incidence of malformations is even greater While in most countries the perinatal mortality has declined during recent decades the mortality from congenital malformations has remained constant representing between 15 to 20 per cent of infant mortality (*Lamy* and *Frézal* 1961)

In spite of these facts the study of congenital malformations was a comparatively neglected field until *Gregg*, an Australian oculist in 1941 demonstrated the relationship between rubella in pregnant women and malformations in their offspring The great importance of environmental influences in the causation of abnormalities has since been confirmed both experimentally and clinically At present it is often difficult to determine in the individual case whether a malformation is inherited or caused by environmental factors operating during pregnancy Only about 20 per cent of the congenital defects appear to be caused by simple Mendelian hereditary factors. Chromosomal aberrations may be found to account for another 10 per cent and only a

The system of classification used was adopted earlier by McIntosh *et al.* (1954) and Takala (1958) and has been exhaustively described in a preliminary report of the investigation (Hedberg *et al.* 1963). In cases where several malformations were present each was generally regarded as a separate malformation.

Congenital heart disease was only registered in those cases which at *post-mortem* examination or after careful clinical observation were found to have definite organic defects in the heart. Infants with transient heart murmurs were not recorded as being malformed. Micro- and hydrocephaly respectively were included when the head circumference exceeded the range of the normal variation for the age. Talipes was recorded when typical equinovarus position of the feet required orthopaedic correction. The live-born malformed infants were as a rule examined by specialists e.g. cardiologists and orthopaedists. Some minor defects of trivial nature were not included for example naevus, hydrocele, accessory auricle etc. Hernias and undescended testes were excluded because they are not generally considered as congenital defects. If there were good reasons to believe that birth trauma was the cause of a congenital defect this has not been recorded as a malformation.

Results of the Study

In the 10,802 pregnancies forming the basis of this report, 267 infants (2.5 per cent) had congenital malformations. Table II shows the types of malformations found in 267 children and is tabulated according to the system of classification mentioned above.

The most common congenital malformations are those of the musculo-skeletal systems but as a rule they are of minor importance in relation to the viability of the child. Malformations of the cardio-vascular system also play prominent role and are of greater importance for survival of the foetus and newborn child and for the future prognosis of the infant. The mortality rate for malformations of different organ systems is shown in Table III. The later deaths tabulated below were all due to the congenital malformation.

Material

The case material includes 11 417 women who visited a Prenatal Care Centre in Gothenburg during pregnancy. For all these women there is a routine form as well as a special card filled out at the first visit to the Centre. These two records formed the starting point for the continued collection of facts concerning the woman and her offspring. In 10,802 cases the pregnancy proceeded to the last trimester and the data on examination of mother and child were considered adequate. In the remaining cases the pregnancy had generally terminated in abortion or the patient had moved away.

All children have been examined by the paediatrician of the Clinic. In all cases of stillbirth and neonatal death *post mortem* examinations have been made at the Pathological Laboratory of the hospital. The subsequent development of the children has usually been followed by a paediatrician at the Children's Welfare Centres and later by a school medical officer. The age of the children at their last examination is seen in Table I.

Table I. *Age of Children at Last Examination*

Age	Number	Percentage
Neonatal period	3948	36.5
1–12 weeks	300	2.8
3– 6 months	719	6.7
7–12 months	1040	9.6
1– 3 years	2636	24.4
More than 3 years	2159	20.0

Definitions

The definition and classification of congenital malformations is difficult. In the present investigation we decided to adhere to the definition of a congenital malformation given by *Schwalbe* (1919). A congenital malformation is accordingly defined as a defect that has developed during foetal life. It is characterized by a change in the structure of one or more organs or organ systems or of the whole body, exceeding the range of variation for the species.

Table III. Mortality Rate of Congenital Malformations by Organ Systems

Organ System	Total	Perinatal Deaths		Later Deaths		Total Deaths	
		Number	Percentage	Number	Percentage	Number	Percentage
Cardio-vascular	64	12	18.8	16	25.0	28	43.8
Central nervous system	43	10	23.3	6	14.0	16	37.3
Gastro-intestinal	43	6	14.0	5	11.6	11	25.6
Genito-urinary	21	4	19.0	4	19.0	8	39.0
Musculo-skeletal	69	3	4.3	2	2.9	5	7.2
Respiratory system	3	1	33.3			1	33.3
Skin	22						
Miscellaneous	2						
Total	267	36	13.5	33	12.4	69	25.9

Age and Parity of Mothers

The present investigation has shown a significantly positive correlation between advanced maternal age and the occurrence of congenital malformations. The incidence of malformed children was thus significantly higher in mothers over 35 years of age. Among the individual defects an association was noted regarding malformations of the cardio-vascular and central nervous system. The latter group included all cases of mongolism.

No general or specific relationship between the occurrence of congenital deformity and parity emerged from the present material.

Family History

Abnormalities in the mother's or in the father's family were recorded in 1.9 per cent of cases where a malformed child was born subsequently. In the control series 0.4 per cent of the women reported abnormalities in the family. These figures are too small to permit statistical analysis. Abnormalities were more often recorded on the mother's side but as only the women were asked about the family history this may explain the apparent pre-

Table II. *Number of Malformations by Organ System and Types*

Types of Malformation	Number	Types of Malformation	Number
I *Cardio-vascular System*	70	Tumour of the kidney	1
Tetralogy of Fallot	2	Adrenocortical tumour	1
Patent ductus arteriosus	4	Hypospadias	9
Coarctation of aorta	7	Epispadias	1
Transposition of great vessels	3	Other malformations of genitals	2
Septal defects	13		
Pulmonary stenosis	2	V *Musculo-skeletal System*	85
Unclassified malformations of the heart	39	Micrognathia	2
		Cervical rib	2
II. *Central Nervous System*	55	Anomaly of clavicle	1
Acrania	4	Malformations of thorax	1
Microcephaly	3	Dysostosis	1
Hydrocephalus	10	Syndactylism	14
Myelomeningocele meningo-encephalocele	8	Polydactylism	6
Other malformations of brain	4	Other malformations of digits	5
Mongolism	20	Malformations of the hip	23
Cataract	3	Talipes	21
Nystagmus	1	Other malformations of extremities	3
Ptosis	1	Congenital amyotonia	1
Other malformations of eye	1	Chondrodystrophy	3
		Arthrogryphosis	2
III. *Gastro-intestinal System*	53		
Cheiloschisis palatoschisis cheilo-gnatho-palatoschisis	30	VI *Respiratory System*	3
Malformations of uvula	1	Choanal atresia	1
Malformations of oesophagus	4	Branchial cyst	1
Malformations of bile ducts	2	Diaphragmatic hernia	1
Malformations of small intestine	6		
Malformations of large intestine	2	VII. *Skin*	25
Malformations of rectum	5	Subcutaneous haemangioma	2
Omphalocele	2	Fibroma	17
Situs inversus	1	Dermoid cyst	1
		Melanoma	1
IV *Genito-urinary System*	23	Malformation of lobule of ear	4
Absence of kidney	3	VIII *Miscellaneous*	2
Malformations of kidney	6	Hemihypertrophy	1
		Haemoglobinopathy	1

Table IV Maternal Condition *Prior to Actual Pregnancy*

Condition	Malformed Children		Controls	
	Number	Percentage	Number	Percentage
Chronic diseases	25	9.5	879	8.5
Endocrine disorders	7	2.7	88	0.8
Syphilis			46	0.4
Adnexal infections	8	3.0	377	3.6
Adnexal tumours	5	1.9	136	1.3
Infections of uterus or vagina	11	3.8	613	5.8
Tumours of uterus or vagina	1	0.4	48	0.4
Operations on adnexa	6	1.4	144	1.4
Obstetric intrauterine operations	32	11.7	1353	12.8
Gynaecologic intrauterine operations	3	1.1	172	1.6

first visit to the Prenatal Care Centre. The aim was to determine whether the maternal condition prior to pregnancy could influence foetal development during pregnancy. Of special interest is the question whether previous disorders of the genital tract could affect the environmental conditions for the foetus in a subsequent pregnancy and thus increase the frequency of malformations.

As seen from the Table the morbidity is about the same among women who later gave birth to malformed children and among the controls. Regarding specific disorders a slight excess of endocrine disorders was reported by mothers of malformed children, but the figures are too small for statistical analysis. Regarding disorders of the genital tract, no difference was found between mothers of malformed children and controls.

Maternal Condition during Pregnancy

The general condition of mothers during pregnancy was carefully followed at the Centres and every mother was repeatedly reminded to record every disorder or accident in her diary.

Of greatest interest is the occurrence of acute infectious diseases during pregnancy and their possible relationship to develop-

dominance of abnormalities on the maternal side The woman is naturally more knowledgeable about her own family than about her husband s

Obstetric History

Previous abortions were reported by 17 1 per cent of the mothers of malformed children and by 12.9 per cent of the women in the control group The difference is statistically significant. The incidence of previous perinatal mortality in the two groups was 3 4 and 2.6 per cent respectively The difference is not significant. Of the mothers of malformed children 3.8 per cent had previously given birth to malformed infants In the control group the corresponding figure was 1.3 per cent. The difference is significant.

Outcome of Pregnancy

Every dead foetus more than 35 cm in length and every foetus showing signs of life at delivery i.e spontaneous breathing, was classified as a child in accordance with Swedish law prevailing during the years 1954–1958

There were 228 perinatal deaths among the children giving a total perinatal mortality rate of 2.1 per cent. The perinatal mortality rate among the malformed children was 13.2 per cent compared with 1 8 per cent in the control series The difference is highly significant.

The incidence of premature infants i e weighing 2500 g or less was 12 per cent in malformed children and 5 1 per cent in the control series. This difference is also highly significant.

There were 191 twin pregnancies but only one of these resulted in a malformed child.

Among the malformed children 57 2 per cent were boys and 42 per cent girls In two cases the sex of the child could not be determined. In the control group 51 7 per cent were boys and 48.3 per cent girls The material thus shows a slight but significant predominance of the male sex among the malformed children.

Maternal Condition Prior to Actual Pregnancy

Data concerning any illness or accident prior to the actual pregnancy were noted on the special card filled out at the woman s

From Table VI no conclusion can be drawn regarding any relationship between various disorders during pregnancy and the occurrence of malformations in the child. Threatened abortion seems to be more common among mothers who later gave birth to malformed children but the difference is not statistically significant.

Placental Anomalies

The incidence of placental infarcts was higher among mothers of malformed children than among controls (5 7 and 2.8 per cent respectively) The difference is statistically significant. Regarding other placental abnormalities no difference was found between the two groups.

Discussion

Most previous investigations on the relationship between maternal health during pregnancy and defects in the foetus have been retrospective after the birth of the child. It is of course difficult to obtain an accurate history of events occurring six to nine months earlier and for this reason every retrospective investigation must include various kinds of error The prospective method of study used in this investigation has many advantages the most important of which is the unbiased nature of the information obtained. Unfortunately a very large series is required to get more reliable data on the incidence of a given defect relative to its antecedent causes.

The results obtained are not directly comparable with those of other workers using data taken retrospectively from hospital records There are however some authors who have made prospective studies of congenital malformations, and it is of particular interest to compare our results with theirs (*McDonald* 1958 *McIntosh et al* 1954)

The incidence of malformations in this series (2.5 per cent) accords with the experience of similar investigations The frequency of reported malformations depends on a great many factors such as the definition of congenital malformation, the frequency of *post mortem* examinations, the length of follow-up time and the accuracy with which the malformations were

Table V *Relation of Abnormality to Infection during Pregnancy*

Infectious Disease	Malformed Children		Controls	
	Number	Percentage	Number	Percentage
Enteritis	4	1.5	91	0.9
Influenza	12	4.5	477	4.5
Measles	1	0.4	50	0.5
Mumps	2	0.8	54	0.5
Whooping cough	1	0.4	29	0.3
Rubella	3	1.2	77	0.7
Varicella			37	0.4
Upper resp infection	42	15.2	1410	13.4

Table VI. *Various Disorders during Pregnancy in Relation to Congenital Abnormality*

Morbid State of Mother	Malformed Children		Controls	
	Number	Percentage	Number	Percentage
Anaemia (Hgb < 60 %)	23	8.3	1008	9.6
Abruptio placentae	1	0.4	14	0.1
Excessive vomiting	1	0.4	90	0.9
Narcosis	4	1.5	94	1.1
Urinary infection	9	3.4	351	3.3
Cholelithiasis	2	0.8	76	0.
Trauma or operation	11	4.2	354	3.4
Threatened abortion	17	6.4	337	3.2
Placenta praevia	1	0.4	26	0.2
Pregnancy toxaemia	16	6.1	570	5.4

mental anomalies in the foetus. During the present investigation epidemics of Asian influenza occurred in Gothenburg. For this reason the frequency of this disease is high but no significant difference was found between mothers of malformed children and controls.

Except for upper respiratory infections the number of cases in the various groups of infectious diseases is too small to permit statistical analysis of the differences between the two groups.

of malformations among live born male infants than among females. In this series the frequency of malformations among male infants was 2.7 per cent against 2.2 per cent among the females. The mechanism by which the sex of the embryo influences the liability to malformations is obscure. The higher incidence of malformations in male infants may be the result of subtle changes in the hormonal environment of the developing embryo

In accordance with most earlier investigations considerably higher perinatal mortality and prematurity rates were found among malformed infants. The differences are highly significant.

Of special interest is the question whether maternal health prior to pregnancy can influence the development of the child. We found as a whole no higher morbidity among mothers of malformed children than among control mothers. Regarding specific disorders the incidence of endocrine diseases was higher in mothers of malformed children but the difference was not significant. As cases of goitre and diabetes constituted the majority of this group the tendency seems very reasonable and the association between these disorders in the mother and malformations in the child has been reported earlier Disorders of the genital tract may theoretically influence the foetal environment in later pregnancies and thereby cause an increased risk of malformations but no such correlation was found in the present investigation.

Since the observation of *Gregg* (1941) that rubella contracted during pregnancy may lead to severe malformations in the child studies concerning the aetiology of congenital malformations have been focused on maternal health during pregnancy The greatest interest has been concentrated on acute infections. Besides rubella a number of virus infections have been associated with congenital malformations *e.g.* herpes zoster mumps, influenza etc. In the present investigation the number of specific infections is too small to evaluate their possible effect on foetal development. Only in cases of influenza and upper respiratory infections has a large series been recorded, but no significant difference was found between mothers of malformed children and the control series. The possible importance of influenza on the aetiology of congenital abnormalities has been pointed out by many authors *e.g.* *Coffey* and *Jessop* (1963) but has been denied by others *e.g.*

registered. *McDonald* (1958) reported an incidence of congenital malformations of 1.5 per cent when only the major abnormalities were considered while *McIntosh* and co-workers (1954) in a very thorough study including even minor abnormalities recorded an incidence of 7.5 per cent. The general distribution of abnormalities agrees with the results of *McIntosh et al.* showing a predominance of musculo-skeletal abnormalities.

A relationship between maternal age and congenital malformations often reported by previous authors has been confirmed by the present investigation showing a tendency toward an increase in the frequency of congenital malformations with advancing maternal age. This increase of malformations with maternal age may be caused by physiologic changes in the aging mother resulting in a poor foetal environment and in production of mutations and chromosomal aberrations (*Penrose* 1939).

No relationship between parity of the mother and malformation of the child was found in this series. Moreover it may be difficult to separate the effect of parity from that of age. The birth of a malformed first born may also influence the willingness of parents to have subsequent children.

An increased incidence of previous abortions in mothers of malformed children has been claimed (*Landtmann*, 1948; *Record* and *McKeown* 1950). In this investigation also there was a significant difference in the reported frequency of previous abortions in mothers of malformed children as compared with the controls. It is possible that the same constitutional characteristic of the mother predisposes both to early death of the embryo and abortion and to malformation of the full term baby.

Of great importance is whether the birth of a malformed child involves a greater risk for a similar result of a future pregnancy. Our investigation has shown that the incidence of previous malformed infants is significantly higher in mothers of malformed children than in the control series. Similar results have been published earlier among others by *Neel* (1961) who also claims the risk of a type-specific recurrence. No increased incidence of malformations among the relatives of mother and father was found in the group of malformed children.

McIntosh and co-workers (1954) reported a higher incidence

formations in the child was found. There was a significant dif ference in the reported frequency of previous abortions and previous malformed infants in mothers of malformed children as compared with the control series The incidence of malformations was higher among male infants than among females. There was a considerably higher rate of perinatal mortality and prematurity among malformed children than among control infants. The mor bidity before and during pregnancy was about the same in mothers of malformed and of normal children. The incidence of placental infarcts was significantly higher in pregnancies resulting in mal formed children. The present series is too small to give reliable information about the importance of any single factor in the aetiology of congenital malformations.

REFERENCES

Campbell W A B Lancet *1* 173 1953

Coffey V P and *Jessop W J E* Irish J. Med. Sci. 349 30, 1955 Lancet *1* 748, 1963

Gregg, N M A. Trans. Ophtal Soc Aust. 3 35, 1941

Hedberg, E Holmdahl K Pehrson S and *Zachrisson U* Acta Paediat. Scand 52, 353, 1963

Lamy M and *Frézal J* First International Conference on Congenital Malformations, Philadelphia, 1961 J B Lippincott Company

Landtman B Arch Dis Child 23 237 1948

M Donald A D New Engl. J Med. 258 767 1958

McIntosh R Merritt K Richards M Samuels M and *Bellows M.* Pediatrics *14* 505, 1954

Neel, J V First International Conference on Congenital Malformations, Philadelphia 1961 J B Lippincott Company

Penrose L S J Ment Sci 85 1141 1939

Record R C and *McKeown T* Brit J Social Med *4* 26, 1950

Schwalbe E L Aschoff Pathologische Anatomie Jena 1919

Takala M E Ann Chir Gynaec Fenn Suppl. 77 47 1958

Received on June 6th, 1966

Campbell (1953) Unfortunately no information is given on the role of influenza in earlier investigations of the prospective type.

No significant association was found between various disorders in the mother during pregnancy and the occurrence of malformations in the child. The incidence of threatened abortion seems to be higher in mothers who later gave birth to a malformed child than among the controls but the difference is not significant. Earlier investigations have yielded conflicting evidence on the association of bleeding during pregnancy and congenital deformity of the infant. *McDonald* (1958) however in a prospective inquiry was not able to find any association between vaginal bleeding during pregnancy and malformations of the child.

Theoretically every anomaly of the placenta may influence the foetal environment especially the supply of oxygen and other metabolites with deleterious consequences for the foetus, a fact which has been shown in a number of experimental investigations. *In this series the incidence of placental infarcts was significantly higher in pregnancies resulting in malformed children than among controls.*

In summary the present series is too small to give reliable information on the importance of any single factor in the aetiology of congenital malformations Malformations probably result from the combined action of several unfavourable factors acting at the same time A very large series is needed to estimate the effect of a single factor genetic or environmental. The present investigation has clearly shown the advantages of the prospective method of study and has contributed to discard some hypotheses regarding the influence of maternal health before and during pregnancy on the development of the foetus.

SUMMARY

The relationship between maternal health and defects in the foetus was studied. A prospective method of study was used and the series included 11 417 pregnant women The incidence of congenital malformations was 2.5 per cent Abnormalities of the musculo-skeletal and cardio-vascular system were predominant. A relationship between maternal age and the occurrence of mal

remaining 49 had survived for periods ranging from 13 hours to 22 days. The mother's antenatal record was carefully studied in each case

The testes were fixed in 10 per cent formol saline and embedded in paraffin. Sections of 5 μ thickness were then taken in the longitudinal axis at 1 mm intervals. All sections were stained with haematoxylin eosin as well as with periodic acid Schiff (Hotchkiss method)

The number of Leydig cells in the testis was calculated by relating the mean number of Leydig cells found in a field of known volume to the volume of the whole testis. The method has been described in detail elsewhere (*Zondek* and *Zondek*, 1965)

A short description of the relevant findings in our previous investigation is indicated.

Summary of Previous Findings

Our previous investigation showed that the number of Leydig cells varied widely from case to case. Detailed analysis revealed the following facts

The mean number of Leydig cells was found to be significantly higher in the toxaemic series than in the controls.

Neither the severity of the toxaemic condition, nor its duration, appeared to influence the number of Leydig cells in the individual case

The controls showed a significant fall in the number of Leydig cells at full-term, but there was no corresponding fall in numbers in the toxaemic series

It was further noted that the number of Leydig cells tended to fall fairly soon after birth, in the toxaemic cases as well as in the controls and independent of the period of gestation. This regression in the number of Leydig cells became gradually apparent about 13–48 hours after birth and was very obvious in the majority of those neonates who had survived for 4–5 days or even longer periods. In view of these findings, none of those cases which had survived for longer than 12 hours was represented on the scatter curves referring to the period of gestation, nor were they included in the statistical evaluations. This was thought necessary in order to avoid any inaccuracies in the representation of the results

It becomes obvious from the above observations that the number of Leydig cells in the individual case has to be assessed according to group (toxaemic or control) time of survival and, in controls also according to period of gestation

Although it was not the scope of our previous investigation to carry out measurements of the individual cell size or to study the histochemical properties of the Leydig cells it was still possible to form an opinion about the

Zondek, Lilly H and Zondek, Theodor Acta obst. et gynec. scandinav 46, 392, 1967
From the Institute of Obstetrics and Gynaecology (Professor J C. McClure Browne) Hammersmith Hospital London England

LEYDIG CELLS OF THE FOETUS AND NEWBORN IN VARIOUS COMPLICATIONS OF PREGNANCY

BY

LILLY H. ZONDEK AND THEODOR ZONDEK

In a previous publication (*Zondek* and *Zondek*, 1965) we have discussed the influence of toxaemia of pregnancy on the testicular Leydig cells of the foetus and newborn and concluded that the mean number of Leydig cells was significantly higher in the toxaemic series than in the controls. At the same time it was noted that there was a wide range of values both in the toxaemias and in the controls and some cases had a very high number of Leydig cells It was therefore decided to investigate whether some special conditions of mother or foetus may have contributed to the high values found in these cases. The present investigation deals with this problem

Material and Method

Our previous investigation was carried out on 59 cases of toxaemia of pregnancy and on 107 control to which have now been added two further cases of toxaemia and 5 controls. Our present survey therefore comprises 61 toxaemic cases and 112 controls. The period of gestation ranged from 27 to 43 weeks in the toxaemic series and from 24 to 42 weeks in the controls. The toxaemic series comprised 32 stillbirths and 29 neonates who had survived for varying periods up to 25 days of life out of these 29 neonates 10 had died within the first 12 hours after birth. Thirty of the controls were stillbirths and 82 were neonates 33 of the neonates had died within the first 12 hours after birth, and the

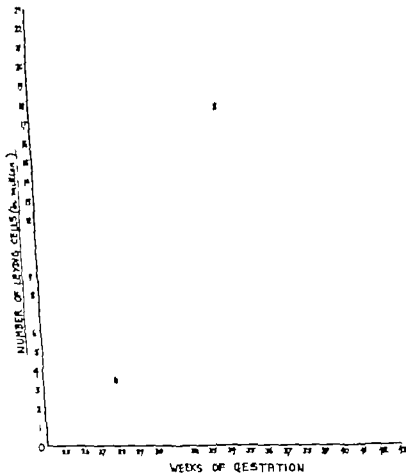


Fig. 1 Number of Leydig cells in 42 toxaemic cases (stillbirths and neonates up to 1 hours of survival) The cases are arranged according to their period of gestation

● cases associated with complications of pregnancy

cases not associated with complications of pregnancy

each of the 6 cases which showed a very high number of Leydig cells (Fig. 2) There were 2 cases of twin pregnancy one of them further complicated by severe hydramnios and 4 cases of accidental haemorrhage

type of cell in the individual case This ranged from large acidophilic cells with a well-marked eccentrically situated nucleus with one or more nucleoli (the large foetal type of Leydig cell) to a smaller type of cell with a reduced amount of cytoplasm and a more elongated oval-shaped nucleus. In general the large foetal type of Leydig cell was noted predominantly in the premature foetus and still remained prevalent in a considerable number of full-term cases of toxaemia of pregnancy The smaller type of cell was prevalent in full-term controls and in all neonates who had survived for certain periods A number of cases presented a mixed picture with intermediate types of cells of various sizes and shapes

In the premature foetus the seminiferous tubules were usually found to be separated by varying amounts of interstitial tissue containing varying numbers of Leydig cells. The seminiferous tubules showed a tendency to be closer together at full-term and the interstitial tissue of the testis was generally reduced in quantity in these cases. The same appearances were noted in premature or full-term children who had lived for a few days and this became even more marked with increasing time of survival. No marked signs of maturation were noted in the tubular epithelium.

Although the mean volume of the testis was found to increase gradually throughout maturation of the foetus, there was a considerable range of volume in each period of gestation. The volume of the right and the left testis in the individual case was found to be either equal or not to differ significantly from each other The mean number of Leydig cells in the two testes was therefore calculated.

Results

Our previous survey was mainly concerned with the number of Leydig cells in toxaemic and non toxaemic cases In our present investigation, the histories of mother and foetus have been further analysed and their possible additional influence on the number of Leydig cells in the individual case has been studied.

The most outstanding feature was that some complication of pregnancy was found to be present in 16 of the 17 cases which showed the highest number of Leydig cells in their group

Of the 5 cases with the highest number of Leydig cells in the *toxaemic series* which were either still born or had died within the first 12 hours after birth, one was a twin in 2 cases there was accidental haemorrhage present and hydrops foetalis with severe hydramnios in the fourth case No additional complication of pregnancy was found in the fifth case (Fig 1) In the corresponding series of *controls* some special clinical feature was present in

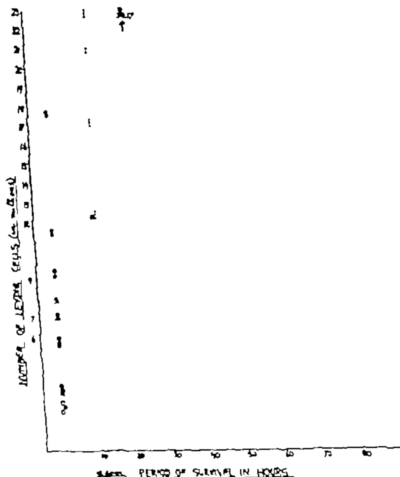


Fig 3 Number of Leydig cells in 58 toxaemic cases (period of gestation 27–43 weeks) The cases are arranged according to their period of survival.
S.B. = stillbirths
● = premature cases associated with complications of pregnancy
▲ = full-term cases associated with complications of pregnancy
= premature cases not associated with complications of pregnancy
= full-term cases not associated with complications of pregnancy

The findings in the 3 toxaemic cases and the 7 controls who had survived for periods varying from 7 to 25 days are not presented on Figs 3 and 4 The number of Leydig cells in these cases ranged from nil to 0 68 millions.

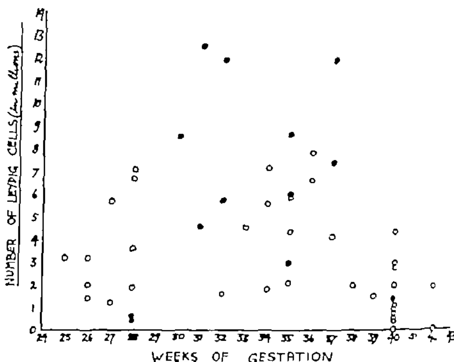


Fig. 2. Number of Leydig cells in 63 *controls* (stillbirths and neonates up to 12 hours of survival) The cases are arranged according to their period of gestation.
● = cases associated with complications of pregnancy
○ = cases *not* associated with complications of pregnancy

Only 2 of the 19 toxaemic cases who had survived for periods longer than 12 hours showed a very high number of Leydig cells, one of them a twin associated with severe hydramnios. The second case was that of a premature child of 37 weeks of gestation which had survived for 22 hours and whose mother was suffering from diabetes mellitus This neonate had the highest number of Leydig cells ever found by us in any of our cases (Fig 3) In the corresponding control group of non toxaemic cases who had survived for periods longer than 12 hours the highest number of Leydig cells occurred in 3 cases of twin pregnancy one of them associated with severe hydramnios (Fig. 5 6 and 7) and in a further case of haemolytic disease without hydrops (Fig 4)

In view of these findings the cases associated with additional complications of pregnancy have been further analysed



Fig. 5. Foetus, aged 32 weeks. Twin. Lived for 2 days and 8 hours. Mother had gross hydramnios. The interstitial tissue shows a large number of Leydig cells. Haematoxylin and eosin. × 150

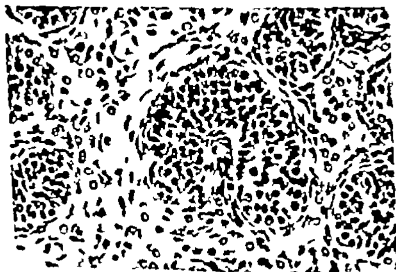


Fig. 6. High power view of Fig. 5. Haematoxylin and eosin. 375

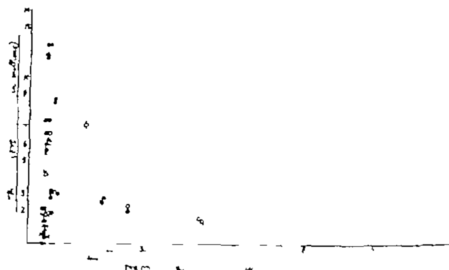


Fig 4 Number of Leydig cells in *105 controls* (period of gestation 24-?? weeks) The cases are arranged according to their period of survival.
S.B. = stillbirths
● = premature cases associated with complications of pregnancy
▲ = full-term cases associated with complications of pregnancy
○ = premature cases *not* associated with complications of pregnancy
× = full-term cases *not* associated with complications of pregnancy

Leydig Cells and Twin Pregnancy

Twenty cases of twins were examined, of these 4 were from 2 sets of twins and for the remainder one twin was obtained from each of 16 sets. Five cases occurred in the toxaemic group while the remaining 15 cases were controls

A high to very high number of Leydig cells was noted in 9 of the 20 twins (45 per cent) medium values in 7 cases (35 per cent) and low values in the remaining 4 cases (20 per cent)

The 2 sets of twins belonged to the control group One of them, a pair of still born twins of 28 weeks of gestation had the lowest number of Leydig cells in their group The mother gave a history of threatened abortion at 17 and 27 weeks of pregnancy and was admitted with bleeding shortly before delivery As will be pointed out later the maternal history may have played a part in the very low number of Leydig cells found in these 2 cases and it was

toxaemic series (5 of 6 cases) than in the controls (5 of 10 cases) It should further be stressed that the highest number of Leydig cells in the whole control group was found to occur in a foetus of 35 weeks of gestation, whose mother had an accidental haemorrhage and also gave a history of toxaemia during her previous pregnancy

Leydig Cells and Haemolytic Disease of the Foetus and Newborn

Hydrops foetalis was present in 4 cases of which 2 occurred in the toxaemic and another 2 in the control group A high to very high number of Leydig cells was found in 2 cases (50 per cent) One of these was associated with toxaemia and severe hydramnios and had the highest number of Leydig cells in his group while the other one was a control. Of the remaining 2 cases one showed a medium (25 per cent) and the other a low value (25 per cent)

Haemolytic disease without hydrops was encountered in 4 cases of which one occurred in the toxaemic group and 3 in the controls. A neonate in the latter group showed a very high number of Leydig cells (25 per cent) This child survived for 60 hours. Medium numbers were present in the remaining 3 cases (75 per cent)

Leydig Cells and Diabetes mellitus

Although there was only one case of diabetes in our investigation this must be described as a remarkable one as it showed the highest number of Leydig cells ever found by us in any of our cases This was a child of approximately 37 weeks of gestation which had survived for 22 hours The mother who also suffered from toxaemia of pregnancy and who gave a diabetic family history had suffered from diabetes for many years. After delivery by Caesarean section, the diabetes became uncontrollable

Leydig Cells and Severe Hydramnios

Severe hydramnios was present in 10 cases of which 4 occurred in the toxaemic series and 6 in the controls. The hydramnios was

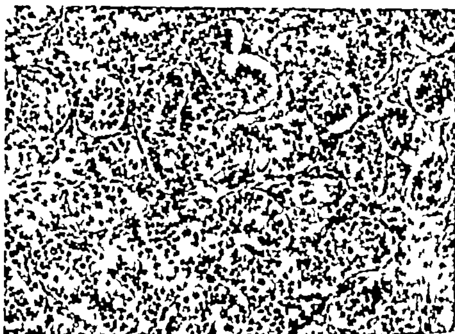


Fig. 7 Foetus aged 35 weeks. Lived for 2 days. Control. The seminiferous tubules lie close together and only a small number of Leydig cells is visible in the interstitial tissue. Haematoxylin and eosin. × 150.

therefore thought advisable to exclude them from the statistical evalution.

The regression of Leydig cells after birth was well demonstrated in the other pair of twins one of whom had survived for 18 and the second one for 72 hours the second one showing lower values than the first.

The findings did not appear to be influenced by the type of twin pregnancy (uni or binovular)

Leydig Cells and Accidental Haemorrhage

In a total of 16 cases (6 toxaemic cases and 10 controls) the mothers had suffered from accidental haemorrhage. A high to very high number of Leydig cells was found in 10 cases (62.5 per cent) medium numbers in 4 cases (25 per cent) and low numbers in 2 neonates (12.5 per cent) It should be noted that the occurrence of high to very high values was more marked in the

toxaemic series (5 of 6 cases) than in the controls (5 of 10 cases) It should further be stressed that the highest number of Leydig cells in the whole control group was found to occur in a foetus of 35 weeks of gestation, whose mother had an accidental haemorrhage and also gave a history of toxaemia during her previous pregnancy

Leydig Cells and Haemolytic Disease of the Foetus and Newborn

Hydrops foetalis was present in 4 cases of which 2 occurred in the toxaemic and another 2 in the control group A high to very high number of Leydig cells was found in 2 cases (50 per cent) One of these was associated with toxaemia and severe hydramnios and had the highest number of Leydig cells in his group while the other one was a control. Of the remaining 2 cases one showed a medium (25 per cent) and the other a low value (25 per cent)

Haemolytic disease without hydrops was encountered in 4 cases of which one occurred in the toxaemic group and 3 in the controls. A neonate in the latter group showed a very high number of Leydig cells (25 per cent) This child survived for 60 hours. Medium numbers were present in the remaining 3 cases (75 per cent)

Leydig Cells and Diabetes mellitus

Although there was only one case of diabetes in our investigation, this must be described as a remarkable one as it showed the highest number of Leydig cells ever found by us in any of our cases This was a child of approximately 37 weeks of gestation which had survived for 22 hours. The mother who also suffered from toxaemia of pregnancy and who gave a diabetic family history had suffered from diabetes for many years. After delivery by Caesarean section, the diabetes became uncontrollable

Leydig Cells and Severe Hyd amnios

Severe hydramnios was present in 10 cases, of which 4 occurred in the toxaemic series and 6 in the controls. The hydramnios was

associated with twin pregnancy in 6 cases and with hydrops foetalis in one case and a very high number of Leydig cells was found to be present in 4 of these latter cases (toxaemic series 2 cases controls 2 cases) The remaining cases showed a medium number of Leydig cells with the exception of a neonate which had survived for 98 hours and had therefore only a very low value

Of particular interest was a full-term twin which had survived for 48 hours. The mother had suffered from toxaemia of pregnancy and also had severe hydramnios The toxaemic signs and symptoms appeared whenever the hydramnios was filling up and disappeared after the fluid had been tapped. Here the child had a very high number of Leydig cells considering that it had survived for 48 hours

It should be stressed that only those cases of hydramnios which were associated with either twin pregnancy or hydrops foetalis, were found to have a very high number of Leydig cells. Hydramnios uncomplicated by any of these complications of pregnancy has therefore not been included in the statistical evaluation.

The above analysis of the results shows that the highest number of Leydig cells was found in cases associated with certain complications of pregnancy such as twin pregnancy accidental haemorrhage diabetes or erythroblastosis foetalis. It further shows that there was also a proportion of other cases which although combined with the same type of complication of pregnancy had only a medium or even a low number of Leydig cells For statistical evaluation the groups of toxaemic cases and controls shown on figure 1 and 2 (stillbirths and neonates up to 12 hours after birth) have therefore been subdivided into cases associated with further complications of pregnancy (complicated cases) and into cases *not* associated with such complications of pregnancy (uncomplicated cases)

In the toxaemic group the number of Leydig cells in the complicated cases varies from 7 22 to 22.94 with a mean of 14 48 whereas in the uncomplicated cases it ranges from 1.51 to 17.90 with a mean of 6 45 (The values with further subdivision into premature and full term cases are shown on Table I) The difference between the mean number of Leydig cells in the com-

Table I. *Range of numbers of Leydig cells in 12 toxaemic cases associated with complications of pregnancy and in 29 toxaemic cases not associated with complications of pregnancy*
(Stillbirths and neonates up to 12 hours of survival. Period of gestation 27–43 weeks.)

	Toxaemic cases associated with complications of pregnancy		Toxaemic cases not associated with complications of pregnancy	
	Range of numbers of Leydig cells (in millions)	Mean number of Leydig cells (in millions)	Range of numbers of Leydig cells (in millions)	Mean number of Leydig cells (in millions)
All cases	7.22 22.94	14.48 (S.D. 4.70)	1.51–17.90	6.45 (S.D. 3.83)
Premature cases	7.22 22.94	14.48 (S.D. 4.70)	2.12 17.90	6.74 (S.D. 4.17)
Full-term cases	no cases	no cases	1.51–8.90	5.68 (S.D. 2.88)

Table II. *Range of numbers of Leydig cells in 15 controls associated with complications of pregnancy and in 45 controls not associated with complications of pregnancy*
(Stillbirths and neonates up to 12 hours of survival. Period of gestation 23–42 weeks.)

	Controls associated with complications of pregnancy		Controls not associated with complications of pregnancy	
	Range of numbers of Leydig cells (in millions)	Mean number of Leydig cells (in millions)	Range of numbers of Leydig cells (in millions)	Mean number of Leydig cells (in millions)
All cases	1.41 13.28	8.44 (S.D. 3.63)	nil–7.90	3.26 (S.D. [illegible].32)
Premature cases	3.04–13.28	8.96 (S.D. 3.28)	1.55–7.90	4.13 (S.D. 2.24)
Full-term cases	1.41 11.45	6.36 (S.D. 5.00)	nil–4.41	1.53 (S.D. 1.32)

associated with twin pregnancy in 6 cases and with hydrops foetalis in one case and a very high number of Leydig cells was found to be present in 4 of these latter cases (toxaemic series 2 cases, controls 2 cases) The remaining cases showed a medium number of Leydig cells with the exception of a neonate which had survived for 98 hours and had therefore only a very low value

Of particular interest was a full term twin which had survived for 48 hours The mother had suffered from toxaemia of pregnancy and also had severe hydramnios. The toxaemic signs and symptoms appeared whenever the hydramnios was filling up and disappeared after the fluid had been tapped. Here the child had a very high number of Leydig cells considering that it had survived for 48 hours

It should be stressed that only those cases of hydramnios which were associated with either twin pregnancy or hydrops foetalis, were found to have a very high number of Leydig cells. Hydramnios uncomplicated by any of these complications of pregnancy has therefore not been included in the statistical evaluation.

The above analysis of the results shows that the highest number of Leydig cells was found in cases associated with certain *complications of pregnancy such as twin pregnancy accidental haemorrhage diabetes or erythroblastosis foetalis.* It further shows that there was also a proportion of other cases which although combined with the same type of complication of pregnancy had only a medium or even a low number of Leydig cells. For statistical evaluation the groups of toxaemic cases and controls shown on figure 1 and 2 (stillbirths and neonates up to 12 hours after birth) have therefore been subdivided into cases associated with further complications of pregnancy (complicated cases) and into cases *not* associated with such complications of pregnancy (*uncomplicated cases*)

In the toxaemic group the number of Leydig cells in the complicated cases varies from 7 22 to 22 94 with a mean of 14 48 whereas in the uncomplicated cases it ranges from 1.51 to 17.90 with a mean of 6 45 (The values with further subdivision into premature and full term cases are shown on Table I) The difference between the mean number of Leydig cells in the com

ble I. *Range of numbers of Leydig cells in 12 toxaemic cases associated with complications of pregnancy and in 29 toxaemic cases ot associated with complications of pregnancy.*
Stillbirths and neonates p to 12 hours of survival. Period of gestation, 27–43 weeks.)

	Toxaemic cases associated with complications of pregnancy		Toxaemic cases not associated with complications of pregnancy	
	Range of numbers of Leydig cells (in millions)	Mean number of Leydig cells (in millions)	Range of numbers of Leydig cells (in million)	Mean number of Leydig cells (in millions)
All cases	7 22 22 94	14 48 (S.D 4.70)	1.51 17.90	6 45 (S.D 3 83)
Premature cases	7 22–22.94	14.48 (S.D 4 70)	2.12 17 90	6 74 (S.D 4.17)
Full-term cases	no cases	no cases	1 51–8 90	5 68 (S.D 2.88)

Table II *Range of numbers of Leydig cells in 15 controls associated with complications of pregnancy and in 45 controls t associated with complications of pregnancy*
(Stillbirths and neonates up to 12 hours of survival. Period of gestation 25–42 weeks.)

	Controls associated with complications of pregnancy		Controls n t associated with complications of pregnancy	
	Range of numbers of Leydig cells (in millions)	Mean number of Leydig cells (in millions)	Range of numbers of Leydig cells (in millions)	Mean number of Leydig cells (in millions)
All cases	1 41 13 28	8 44 (S.D 3.63)	nil– 90	3 26 (S.D 2 32)
Premature cases	3 04–13 28	8 96 (S.D 3 28)	1 55–7 90	4 13 (S D 2 24)
Full-term cases	1 41–11 48	6 36 (S.D 5 00)	nil–4 41	1 53 (S D 1 32)

Table III. *Statistical difference between mean number of Leydig cells in various groups of toxaemias and controls*

Group	Group	Difference between mean number of Leydig cells
Toxaemic cases associated with complications of pregnancy	Toxaemic cases not associated with complications of pregnancy	Significant ($P < 0.001$)
Controls associated with complications of pregnancy	Controls not associated with complications of pregnancy	Significant ($P < 0.001$)
Toxaemic cases associated with complications of pregnancy	Control associated with complications of pregnancy	Significant ($P < 0.001$)
Toxaemic cases not associated with complications of pregnancy	Controls not associated with complications of pregnancy	Significant ($P < 0.001$)
Toxaemic cases not associated with complications of pregnancy	Controls associated with complications of pregnancy	*Not* significant ($0.20 > P > 0.10$)

plicated and uncomplicated cases of the toxaemic group is statistically significant ($P < 0.001$) (Table III) This also applies to comparison between complicated and uncomplicated premature toxaemic cases There were no complicated full term cases in the toxaemic group except for a case with hydramnios which has not been included in the statistical evaluations (see above)

In the controls the number of Leydig cells in the complicated cases ranges from 1.41 to 13.28 with a mean of 8.44 whereas in the uncomplicated cases it varies from nil to 7.90 with a mean of 3.26 (The values after further subdivision into premature and full term cases are shown on Table II) The difference between

the mean number of Leydig cells in the complicated and uncomplicated controls is statistically significant ($P < 0.001$) (Table III) Similar results are obtained when analysing premature and full-term controls separately

The difference between the mean number of Leydig cells in the toxaemic group and the controls is shown on Table III. It is apparent that the mean number of Leydig cells in the complicated toxaemic group is significantly higher than in the complicated controls ($P < 0.001$) The same result is obtained when comparing the uncomplicated toxaemic cases with the uncomplicated controls ($P < 0.001$)

The mean number of Leydig cells in the toxaemic cases *not* associated with further complications of pregnancy however does not differ significantly from the mean number of Leydig cells in the controls which are associated with such complications of pregnancy ($0.20 > P > 0.10$) (Table III) Similar results are obtained when comparing premature and full-term groups separately

We have previously demonstrated that, whereas there was a significant fall in the mean number of Leydig cells at full term in the controls, there was no corresponding regression of their numbers in the toxaemic series. Further analysis of our present findings reveals however that the controls associated with special complications of pregnancy show no significant fall in the mean number of Leydig cells at full-term ($0.40 > P > 0.30$)

The type and appearance of the Leydig cells at different periods of gestation as well as after birth, have already been described (see summary of previous findings) It should, however be stated that those cases with additional complications of pregnancy which had survived for periods up to about 2 1/2 days and which showed a very high number of Leydig cells, usually presented a mixed picture with intermediate types of cells of various sizes and shapes

Discussion

The results of our present investigation demonstrate the important influence of certain complications of pregnancy on the number of Leydig cells in the foetal and neonatal testis. One of these complications, namely toxaemia of pregnancy has already been

Table III. *Statistical difference between mean number of Leydig cells in various groups of toxaemias and controls*

Group	Group	Difference between mean number of Leydig cells
Toxaemic cases associated with complications of pregnancy	Toxaemic cases *not* associated with complications of pregnancy	*Significant* ($P<0.001$)
Controls associated with complications of pregnancy	Controls *not* associated with complications of pregnancy	Significant ($P<0.001$)
Toxaemic cases associated with complications of pregnancy	Control associated with complications of pregnancy	Significant ($P<0.001$)
Toxaemic cases *not* associated with complications of pregnancy	Controls *not* associated with complications of pregnancy	Significant ($P<0.001$)
Toxaemic cases *not* associated with complications of pregnancy	Controls associated with complications of pregnancy	*Not significant* ($0.20>P>0.10$)

plicated and uncomplicated cases of the toxaemic group is statistically significant ($P<0.001$) (Table III) This also applies to comparison between complicated and uncomplicated premature toxaemic cases There were no complicated full term cases in the toxaemic group except for a case with hydramnios which has not been included in the statistical evaluations (see above)

In the controls the number of Leydig cells in the complicated cases ranges from 1.41 to 13.28 with a mean of 8.44 whereas in the uncomplicated cases it varies from nil to 7.90 with a mean of 3.26 (The values after further subdivision into premature and full term cases are shown on Table II) The difference between

High to very high numbers of Leydig cells were present in 2 of our 4 cases with hydrops foetalis. One of these 2 cases was further complicated by toxaemia and severe hydramnios. *Scott* (1958) found an incidence of toxaemia of pregnancy of 66 per cent in 249 published cases of hydrops foetalis including 52 of his own. According to *Browne* and *Browne* (1960) there is no evidence that pregnancy toxaemia is more frequent than usual in haemolytic disease apart from hydrops foetalis in which the incidence is much increased. *Jones* and *Duncan* (1964) report the occurrence of the toxaemic type of maternal syndrome in 20 cases (59 per cent) in a series of 34 cases of hydrops foetalis. In view of the observations of the above mentioned authors it is of interest to note that a very high number of Leydig cells was present in only one of our 4 cases with haemolytic disease *with*out hydrops and that this finding may have been due to chance.

The special liability of pregnant diabetics to develop toxaemia of pregnancy is well recognised (*White* 1939, *Mengert et al.*, 1939, Bill and Posey 1944 and others).

Some authors believe that there is an increased incidence of toxaemia of pregnancy in cases of hydramnios (*van der Velden* 1957 and others). *Jeffcoate* (1959) however reports an incidence of toxaemia in 11 of 21 cases with hydramnios complicated by multiple pregnancy, diabetes or hydrops foetalis (52 per cent), whereas in 148 cases of uncomplicated hydramnios, toxaemia occurred only 16 times. He concludes that hydramnios per se is not associated with an increased incidence of toxaemia and that in series reported in the literature which suggest the contrary as well as in his own cases, the explanation is the inclusion of causal conditions such as twin pregnancy, diabetes and hydrops foetalis which in themselves may favour toxaemia. It is, therefore, of interest that high numbers of Leydig cells were found to be present in only those cases of hydramnios where this was further complicated by twin pregnancy or hydrops foetalis and this refers to the toxaemic series as well as to the controls. In view of these observations one may speculate whether there exists a common factor in all the above described conditions including toxaemia of pregnancy.

It is generally assumed nowadays that the foetal Leydig cells

discussed in a previous publication (*Zondek* and *Zondek* 1965) when it was demonstrated that the number of Leydig cells was significantly higher in the toxaemic series than in the controls.

Our present survey deals with cases showing complications *such as multiple pregnancy accidental haemorrhage rhesus in*compatibility and diabetes mellitus. It is striking that cases associated with such special clinical features tended to have a higher number of Leydig cells than cases not associated with such features It is also noteworthy that the highest values were encountered in a proportion of cases which showed a combination of toxaemia with one of the above mentioned conditions and that the mean number of Leydig cells in this group of cases was significantly higher than in the corresponding group of controls.

If however the controls were complicated by any of the above named conditions the mean number of Leydig cells did not differ significantly from that of the toxaemic group of cases which were *not* complicated by such conditions. It is therefore suggested that these special clinical features may have had an effect on the foetal testis similar to toxaemia of pregnancy

In view of the above observations it is of interest to consider any possible relationship between toxaemia of pregnancy and conditions such as multiple pregnancy accidental haemorrhage rhesus incompatibility and diabetes

Pre-eclamptic toxaemia and eclampsia are more likely to develop in women who have multiple pregnancies (*Johnstone* 1961) According to *Browne* and *Browne* (1960) the liability to eclampsia in twin pregnancy is four or five times that in a single pregnancy The same authors also report that toxaemia of pregnancy is present in about 90 per cent of cases of accidental haemorrhage In this connection it is of interest that a high or very high number of Leydig cells was more frequently encountered in those of our cases with accidental haemorrhage which occurred in the toxaemic group (5 of 6 cases) than in those occurring in the controls (5 of 10 cases) It is also noteworthy that the highest number of Leydig cells in our control cases was found in a foetus whose mother had an accidental haemorrhage and who also gave a history of toxaemia during her previous pregnancy

stages of multiple pregnancy According to *Jeffcoate* and *Scott* (1959) there is an obvious quantitative increase of chorionic tissue and also well established evidence of increased function in multiple pregnancy revealed by the output of HCG The latter may be so high as to cause difficulty in distinguishing twins from hydatidiform mole in some cases. *Gemzell* (1963) found that the excretion of HCG was elevated in a few cases of multiple pregnancy His observations in a case with quadruplets are of particular interest. This patient was followed up throughout pregnancy and she excreted about 10 times as much HCG as normal during the second and third trimester of pregnancy Of the 6 twin pregnancies described by *Goplerud* and *Bradbury* (1965) one had a raised level of HCG in the 23rd week and two in the third trimester whereas normal levels were found in the remaining 3 patients. The same authors noted that in 2 patients who had three sets of triplets, the levels of HCG were raised in the third trimester *Jacobowitz* (1964) reports serum gonadotrophin titres of unusual height during the first trimester in 2 cases of triple pregnancy and in one of these the high levels were present until late in the second trimester It should be noted here that all our cases of twin pregnancy had reached the third trimester

Jeffcoate and *Scott* (1959) recorded that some conditions associated with a high incidence of pre-eclampsia (hydrops foetalis maternal diabetes mellitus and hydatidiform mole) were characterised by an unduly large mass of placental tissue with abnormal persistence or re-awakening, of the Langhans layer and excretion of increased amounts of HCG Increased excretion of gonadotrophin in association with hydrops foetalis was already described by *Herrnberger* (1940) and *Zsigmond* (1941) More recently *Goplerud* and *Bradbury* (1965) reported raised levels of HCG in this condition which they found in the third trimester of gestation in 12 of 17 patients who were delivered of stillborn or liveborn infants with hydrops foetalis. Nine of these 17 patients also had severe hydramnios 7 with elevated levels of HCG

There was only one case of diabetes mellitus in our investigation which occurred in a toxaemic mother However this case was remarkable in so far as it had the highest number of Leydig

are formed by the interstitial tissue of the foetal testis in response to its stimulation by human chorionic gonadotrophin (HCG) with its marked interstitial-cell stimulating activity (*Kupperman* 1963 and others) The dependence of these cells on the presence of a maternal or placental hormonal influence is further proved by their spectacular fall in numbers after birth *i.e.* after removal of the foetus from its intrauterine environment.

There are various reports in the literature that excretion of increased amounts of HCG does occur in a proportion of cases with toxaemia of pregnancy (*Smith* and *Smith* 1934 *Taylor* and *Scadron* 1939 *Loraine* and *Mathews* 1950 *B Zondek* and *Pfeifer* 1959 and others) It has therefore, been suggested by us that the large number of Leydig cells found in a proportion of the toxaemic cases in our previous investigation may have been due to a raised level of HCG The recent observations of *Lauritzen* and *Lehmann* (1965) tend to confirm our conclusions. These authors measured the 24-hourly urinary output of HCG in 30 healthy neonates during the first few days of life They found that whereas there was a measurable, though relatively low excretion of HCG within the first 24 hours of life in only 7 of 21 children from normal mothers HCG was excreted in relatively high amounts by 7 out of 9 children from toxaemic mothers who themselves showed a raised urinary level of HCG The excretion of HCG decreased rapidly during the second and third day of life and could no longer be measured on the 4th day after birth. This latter observation is also reflected by the rapid disappearance of Leydig cells after birth in our own cases

The placenta is often abnormal in toxaemia of pregnancy but, although this will not be discussed here in detail it should be noted that macro- and microscopic changes suggestive of functional hyperactivity have been described to occur in a proportion of such cases (*Jeffcoate* and *Scott* 1959 *Wigglesworth* 1962, and others)

With regard to the findings in some cases of our present investigation it is of interest to note that raised levels of HCG have been reported to occur in most of the conditions which we found to be associated with a high or very high number of Leydig cells. Values of HCG above normal have been described at various

foetuses. Moreover we found that the number of Leydig cells was raised in only a proportion of foetuses and neonates of such mothers and this is borne out by the above cited statements that increased levels of HCG are only encountered in a certain per centage of such patients.

The possibility of a cumulative effect of combined conditions, such as e.g. toxaemia and multiple pregnancy on the foetal testis, as shown by the very high number of Leydig cells in a proportion of these cases has to be considered. One may even speculate that the simultaneous presence of toxaemia and an additional com plication of pregnancy could have produced an even higher level of HCG in these cases. In this connection it is of interest that *Jeffcoate* and *Scott* (1959) who carried out quantitative Aschheim-Zondek tests in 6 cases of hydrops foetalis late in pregnancy i.e. at the time when the excretion of gonadotrophin is normally low not only obtained a positive reaction in each case but also noted a suggestion of a correlation between the intensity of the reaction and the occurrence of toxaemia.

In contrast to the above discussed conditions and their frequent association with a raised level of HCG it is of interest to note that *Gemzell* found quantitative determination of HCG to be of great help in his cases of threatened abortion as the levels were low in cases where the abortion was inevitable. Attention should, therefore be drawn to the observation of this author in view of the very low number of Leydig cells in a pair of stillborn twins where the mother gave a history of threatened abortion at 17 and 27 weeks of gestation and was admitted at 28 weeks with severe bleeding shortly before delivery

In conclusion it may be stated that conditions which in a number of cases predispose to or complicate toxaemia of pregnancy (multiple pregnancy accidental haemorrhage hydrops foetalis and diabetes mellitus) may have been responsible for the high number of Leydig cells in the testes of some of these foetuses and neonates possibly by raising the level of HCG It is, therefore suggested that not only toxaemia of pregnancy but also the conditions which may be connected with it, should be considered as potential interstitial-cell-stimulating factors.

cells ever recorded by us It is of interest to note that *Bryer* (1942) also referred to hyperplasia of testicular interstitial cells in a full term still born foetus of a diabetic mother who had shown signs of toxaemia during late pregnancy and had an eclamptic fit at birth. *Driscoll et al* (1960) reported similar appearances in the testes of 9 of 24 babies (38 per cent) born to diabetic mothers and presumed this to be an effect of a high titre of HCG on the foetus Similar findings were recorded by *Geoghegan* and *Drury* (1962) in one case, and in all 7 babies examined by *Scott* (1962) Such testicular appearances, however were not noted by *Rewell* (1962) in his cases of perinatal death associated with maternal diabetes.

The gonadotrophin output is often abnormally high in diabetic pregnancy and this was demonstrated by *Smith* and *Smith* (1940) More recently *Loraine* (1958) recorded that in such cases the mean placental concentration of HCG was significantly higher than in normal subjects He also found that about 30 per cent of these patients showed abnormally high levels of HCG in the serum and urine *Goplerud* and *Bradbury* (1965) reported raised levels of HCG in the third trimester of gestation in 9 of 44 pregnancies in 34 diabetic women.

No reference could be found in the literature with regard to testicular Leydig cells in conditions such as accidental haemorrhage multiple pregnancy haemolytic disease and hydramnios, nor have we been able to find any report regarding HCG levels in non toxaemic women suffering from accidental haemorrhage.

We have already suggested that, in the controls conditions such as multiple pregnancy accidental haemorrhage and hydrops foetalis may have had a stimulating effect on the interstitial tissue of the foetal testis *similar to toxaemia of pregnancy* (Our findings in erythroblastosis without hydrops however are not conclusive) It is therefore of great interest that these conditions are so frequently found to be connected with toxaemia of pregnancy If one relates our findings in these cases to the further observations of the above mentioned authors one may therefore suggest a causal relationship between a raised *level of HCG* which has been reported to occur in mothers suffering from these conditions and the increased formation of Leydig cells by their

REFERENCES

Bayer J Virch. Arch. 308 659 1942
Bill, A. H and Posey F M. J Amer J Obstet. Gynec. 48 405, 1944
Browne F J and Browne J C McClure Antenatal and Postnatal Care, 9 ed. J & A Churchill, London 1960
Driscoll S G. Benirschke K., and Curtis G W Amer J Dis Childh. 100 818, 1960
Gemzell, C Personal communication, 1963
Geoghegan, F and Drury M. L, Lancet 1 1243, 1962
Goplerud C. P and Bradbury J T Amer J Obstet Gynec. 91 23 1965
Harris G. H Barr A and Stevenson A. C J Obstet. Gynaec. Brit. Cwlth 68 800, 1961
Hornberger K Arch. Gynäk. 170 287 1940
Jacobowitz W E Obst. and Gynec. 23 788, 1964
Jeffcoate T N A and Scott J S. Amer J Obstet Gynec. 77 745 1959
Jones A Howard and Duncan A S. J Obstet. Gynaec. Brit. Cwlth 71 61 1964
Johnstone R. W A Textbook of Midwifery for Students and Practitioners, 20 ed. A & C Black, London 1963
Kupperman H S Human Endocrinology 2 vol. Davis, Blackwell Scientific Publishers, Oxford 1963
Lauritzen C and Lehmann W D Arch. Gynäk. 200 578, 1965
Loraine J A and Mathews G D J Obstet. Gynaec. Brit. Emp 57 542, 1950
Clinical Application of Hormone Assay Livingstone, Edinburgh and London 1958
Mengert W F and Laughlin K. A. Surg Gynec. & Obst. 69 615 1939
Revell R. E Lancet 2 153 1962
Scott J M Lancet 2 100, 1962
J Obstet Gynaec Brit Emp 65 689 1958
Smith G V and Smith O W Amer. J Physiol 107 128, 1934
Smith O W and Smith G. V Amer J Obstet. Gynec. 39 405, 1940
Taylor J H C and Scadron E. N Amer J. Obstet. Gynec. 37 963, 1939
Van der Velden W H M Thesis University of Amsterdam, 1957
Wigglesworth J S J Obstet. Gynaec Brit. Cwlth. 69 355, 1962
Zondek B and Pfeifer V Acta obst. et gynec scand. 38 74., 1959
Zondek L H and Zondek T Biol Neonat 8, 1 1965
Zugmond Z Z Gynäk 65 1258, 1941

Received on June 1st, 1966

SUMMARY

As described in a previous investigation we found that the mean number of testicular Leydig cells was significantly higher in foetuses and neonates from mothers suffering from toxaemia of pregnancy than in controls We have suggested that this may have been due to a raised level of HCG

The problem has been re-investigated and it has been found that in the toxaemic series as well as in the controls, cases associated with some special complications of pregnancy such as multiple pregnancy accidental haemorrhage hydrops foetalis and diabetes mellitus tended to have a higher number of Leydig cells *than cases not associated with such complications* All these conditions frequently predispose to or complicate toxaemia of pregnancy and raised levels of HCG have been recorded to occur in most of them.

The highest numbers of Leydig cells were found in some of those cases which showed a combination of toxaemia with one of the above mentioned complications of pregnancy

It has therefore been suggested that not only toxaemia of *pregnancy but also the conditions which may be connected* with it should be considered as potential interstitial-cell-stimulating factors

Acknowledgements

We are much indebted to Professor J C McClure Browne for giving us the opportunity to undertake this investigation and for his advice with regard to some obstetrical problems. We are also very grateful to Professor C V Harrison for granting us facilities in his department. Our grateful thanks are due to all those pathologists obstetricians and paediatricians to whom we have already expressed our thanks in previous publications. Dr R. Doll and Dr W J Martin, Statistical Research Unit University of London have kindly assisted us in the statistical evaluation of the results and we are most grateful for their help

Two days before the operation the patients were given Dextran 40 (10% in glucose) intravenously in a dose of 10 ml per kg body weight. One day before the operation they were given 5 ml of Dextran 40 per kg body weight and an equal dose was given during the hour before the beginning of the actual operation. Samples of amniotic fluid, umbilical cord blood and venous blood were obtained during the operation. Sodium citrate was added to each sample of blood and the plasma was analysed for dextran.

Group II

This group consisted of 8 normal women delivered at term without complications, one patient with severe toxemia of pregnancy and delivered by Caesarean section at term, and one patient who was delivered by vacuum extractor All were given 500 ml of Dextran 40 two to three hours before delivery The infusion time was one hour and a half Venous blood was obtained from the mother and from the umbilical cord at delivery Samples were treated in the same way as in Group I.

Group III

This group consisted of 7 normal patients delivered at term without complications. The women were given 400–800 ml of Dextran 70 (10% in glucose) two to eight hours before delivery Infusion time was one to two hours. Blood samples were obtained and analysed in the same way as in Group II.

The chemical method used was the o-toluidine method of *Redéi* and *Nagy* (1961) For control, the anthron method of *Wallenius* (1953) and the copper sulphate method by *Hint* and *Thorsén* (194) were also used in some cases. Corrections were made for glucose Duplicate estimations were always performed. The o-toluidine method can demonstrate dextran down to 1.5 mg/100 ml and the anthron method down to 2 mg/100 ml. According to *Borell* and *Åberg* (1955) the sensitivity of the *Hint* and *Thorsén* method is rather low To check the accuracy of the methods, known amounts of Dextran 40 were added to umbilical cord blood and estimated. The added dextran was always quantitatively found in these analyses

Falk, Viking, Forkman Bodil and Arfors, Karl-E., Acta obst. et gynec. scandinav. 46, 414, [illegible]

From the Department of Obstetrics and Gynaecology (Professor Sig Kullander) Malmö General Hospital Malmö and the Department of Experimental Medicine AB Pharmacia Uppsala Sweden

THE PERMEABILITY OF THE PLACENTA TO DEXTRANS

BY

VIKING FALK, BODIL FORKMAN AND KARL-E. ARFORS

It is widely agreed that small molecules can pass through the placenta (for ref see surveys by *Hagerman* and *Villee* 1960; *Marx* 1961 *Baker* 1960) However opinions differ regarding the permeability of the placenta to large molecules. *Vara* (1950) found no dextran in umbilical cord blood when pregnant women were given 500 ml dextran VII E (Macrodex® 6 %) three hours before delivery On the other hand *Borell* and *Aberg* (1955) found that when the concentration of dextran in the maternal blood reached 0.25 g/100 ml some dextran passed across the placental barrier They thought that is was probably that portion of the dextran VII E of low molecular weight which passed into the foetal circulation. Clinical dextran of the Leuconostoc mesenteroides VII E type used by them had, however a higher average molecular weight and a higher degree of branching than the dextrans used at present *i e* Dextran 70 (Macrodex® average molecular weight 70 000) and Dextran 40 (Rheomacrodex® average molecular weight 40 000)

The aim of this study was to ascertain whether Dextran 40 (Rheomacrodex® 10 % in glucose) passes through the placental barrier and during the course of this investigation we also included a study of Dextran 70

Material and methods

Group I

This group consisted of 8 pregnant women awaiting legal abortion by abdominal hysterotomy at 17 to 20 weeks gestation.

can readily pass through the placenta even if the mechanism and the exact site of the passage is unknown. This transfer can hardly be a question of diffusion (*Berger* and *Novik* 1964) *Gelfand et al.* (1960) concludes that there is no relationship between molecular size or weight of the substance transferred and its rate of permeation. It is suggested by *Dempsey* (1954) that movement of large molecules across the placenta takes place by pinocytosis.

Only few publications are available on the passage of synthetic high molecular weight polymers through the placenta and even these few are contradictory Thus, according to *Posner et al* (1953) polyvinylpyrrolidone (PVP) passes the placenta by simple diffusion but according to *Jozsef et al.* (1956) it does not. *Vara* (1950) studied the dextran content in umbilical blood in two cases of toxemia in late pregnancy where the mothers were given 500 ml of dextran VII-E 3 hours before delivery He found no dextran in the foetal circulation. On the other hand, while studying the disappearance rate of dextran VII-E from the blood of healthy pregnant women just before delivery *Borell* and *Åberg* (1955) found that the dextran passed through the placental barrier if the maternal concentration reached 0.25 g per 100 ml plasma. In the present investigation we found no evidence of transfer of dextran molecules across the placental barrier even though the concentration of dextran in the patients plasma was between 0 13 and 0 74 g per 100 ml.

Page (1957) postulated that if the concentration in the circulation is high enough almost any substance can cross the placental barrier with time though not always in amounts large enough to cause any demonstrable physiological or pharmacological effect. But in cases in Group I in which Dextran 40 was given repeatedly for 48 hours before the operation and sampling, by which time the concentration of the dextran in the blood was fairly high, no dextran was found in the umbilical cord plasma.

Dextran 40 and 70 are used as flow improvers in various clinical conditions. Judging from our findings such dextrans can hardly have any effect on the foetus and can therefore be given without hesitation to pregnant women.

Results

The concentration of dextran found in maternal venous plasma varied with the volume infused, the infusion rate and the interval between the infusion and collection of the sample i.e.

Group I Venous plasma mean concentration 426 mg per 100 ml (340–500 *mg/100 ml*)
Umbilical cord plasma negative, *i.e.* no dextran found
Amniotic fluid negative

Group II Venous plasma mean concentration 310 mg/100 ml (190–520 mg/100 ml)
Umbilical cord plasma negative

Group III Venous plasma mean concentration 440 mg per 100 ml (130–740 mg/100 ml)
Umbilical cord plasma negative

In some cases the concentration of dextran in the patient's plasma and in umbilical cord plasma were estimated simultaneously by the anthron, o-toluidine and copper sulphate methods (Table I)

Table I. *The Concentration of Dextran in Venous Blood Plasma and in Umbilical Cord Plasma Simultaneously Estimated by the Anthron O-toluidine and Copper Sulphate Methods in 3 Patients*

Patient		O-toluidine *mg/100 ml*	Anthron *mg/100 ml*	Copper sulphate mg/100 ml
No 1	Venous blood plasma	480	650	650
	Umbilical cord plasma	neg	neg	neg
No. 2	Venous blood plasma	370	480	430
	Umbilical cord plasma	neg	neg	neg
No 3	Venous blood plasma	440	520	530
	Umbilical cord plasma	neg	neg	neg

Discussion

It is now well established that body macromolecules, such as gammaglobulins, with a molecular weight of 150 000 to 200 000

Starup, J. Acta obst. et gynec. scandinav. 46, 418, 1967
From the Department of Gynaecology and Obstetrics (E. Østergaard, M.D.) and the Department of Pathology (S. Fischer, M.D.), Frederiksberg Hospital Copenhagen, Denmark

ENDOMETRIAL HISTOLOGY AND VAGINAL CYTOLOGY DURING ORAL CONTRACEPTION

BY

J. STARUP

During recent years the number of orally active gestagens has been constantly increasing, and these steroids are now widely used both for the treatment of certain gynaecological disorders and for contraceptive purposes. The oral contraceptives in current use are composed of a synthetic oestrogen and a synthetic gestagen, and this combination is given cyclically from day 5 to day 24 of the menstrual cycle. The widespread use of these compounds has naturally furthered the interest in their effects on the endometrium and the vaginal epithelium, which are both easily accessible end-organs, and react quite sensitively and characteristically to hormones.

The endometrium under influence of oral contraceptives has been studied quite extensively by several authors (*Durkin et al.* 1965, *Flowers* 1964, *Grant* 1964, *Jackson* 1963, *Larsen* 1964, *Lin et al.* 1964, *Maqueo et al.* 1963 and 1964, *Mears* 1965, *Pincus et al.* 1958, *Rice-Wray et al.* 1963, *Roland* 1958, *Roland et al.* 1964). The majority of investigators has found that the endometrial changes which occur during treatment with these steroids are in some ways characteristic for the various main types of gestagens, though the changes are mainly very similar.

The same is true of the vaginal epithelium measured as the changes in the cornification index (C.I.) and in the karyopyknotic index. Here, too, the picture changes in a characteristic manner depending on the main type of gestagen chosen, although

SUMMARY

Pregnant patients in various stage of gestation were given Dextran 40 (Rheomacrodex®) and Dextran 70 (Macrodex®) without any demonstrable passage through the placenta.

REFERENCES

Baker J B. E. Pharmacol. Rev 12 37 1960
Berger M and *Norik O* Fortschr Geburtsh. Gynäk. 17 30 1964
Borell U and *Aberg, B* Acta obst. et gynec. scandinav 34 75 1955
Dempsey E. W In Flexner Gestation. Trans. 1st Conf Josiah Macy Jr, Found. New York 1954
Gelfand M M Strean G J Pavilanis V and *Sternberg, J* Am. J. Obst. & Gynec. 79 117 1960
Hagerman D D and *Villee C. A.* Physiol. Rev 40 313 1960
Hint H and *Thorsén G.*, Acta chem. scandinav 1 808, 1947
Jozsef F Jozsef B. and *Dancshazy M* Orvosi Hetilap 97 218 1956
Marx G F Anesthesiology 22 294 1961
Page E. F Am. J Obst. & Gynec. 74 705 1957
Posner A. C., Cordice J W V Jr and *Scudder J* Surg. Gynec. Obstet. 96 581 1953
Redel A. and *Nagy S* Nature 191 173 1961
Wallenius G., Acta Soc. Med. Upsalien. 59 69 1953
Vara P Acta obst. et gynec. scandinav 0 Suppl. 6, 1950

Received on Aug. 10th, 1966

obtained during a control cycle immediately after cessation of medication. During the control cycles the smears were begun at the end of one menstrual period and taken every day until the start of the next. During the treatment-cycles the slides were examined on the day of the first tablet and were taken every day thereafter until the next bleeding occurred. The films were fixed in alcohol and ether and stained by the Shoor hematoxylin method. For evaluation we have used the C.I (*Allende* and *Orias* 1950 *Pundel* 1952) Instead of registration of the change in the C.I. which occurs day by day throughout the cycle, we have according to *Jackson* and *Linn* (1964) plotted the extremes of C.I. (high and low) as a straight vertical line the mean being indicated by a small horizontal line placed on the vertical line, representing the range.

Results

We found that the endometrial response was almost independent of the numbers of the treatment-cycles Thus, biopsies obtained on the same cycle day but after a varying period of treatment showed very similar patterns.

Figs. 1 to 6 show typical stages in the endometrial changes during the cycle Submuclear vacuolization, which is the earliest sign of secretory activity appears in the glandular epithelial cells as early as day 8 (3 days after the onset of therapy) With continued drug administration the number and size of subnuclear vacuoles increase and reach a maximum about days 10 to 12. Subsequently the vacuoles become supranuclear in position for a very short time before ultimately discharging secretion in the glandular lumen. The amount of intracellular or intraluminal secretion is always small. In spite of the secretion the glands do not increase in size and only slight tortuosity develops The secretory activity appears to reach a maximum on days 13 to 15 but the endometrial glands tend to resemble those seen around days 19 to 20 of a normal untreated cycle. Thus, the early secretory activity never progresses to a full-blown picture as seen in the normal untreated cycle and the result is an shortl secretory phase. Around days 16 to 17 the glands begin

the differences are very small. This was found for instance by *Jackson* and *Linn* (1964)

The purpose of the present investigation is to give a description of the changes in the endometrium and in the vaginal epithelium during cyclical treatment with Delpregnin® (each tablet contains 5 mg of megestrol acetate +0.1 mg of mestranol)

Materials and Methods

The patients in this study were fertile gynaecologically normal women and were aged 18 to 34 All patients were treated for contraceptive purposes and received a daily dose of 5 mg of megestrol acetate +0.1 mg of mestranol cyclically from day 5 through day 24 of the cycle Two groups of patients were studied.

The first group consisted of 76 women aged 18 to 34 who had been treated cyclically with Delpregnin for a period of 1 to 16 months In each patient endometrial biopsies were obtained two or three times during the treatment period at various times during the cycle and after various numbers of treatment-cycles. A total of almost 200 biopsies were available for examination, and from these a number yielding a satisfactory cross section of representative stages of the cycle were selected for a detailed study One third of the biopsies was obtained during the first treatment-cycle, and the remainder of the biopsies was almost equally distributed over the following treatment-cycles. Tissues were fixed in formalin or alcohol blocked and sectioned, and stained with hematoxylin-eosin and Schiff stain for mucopolysaccharides The major features considered were the development of the endometrial glands, the presence or absence of secretion and the presence of oedema and predecidual reaction in the stroma.

The second group consisted of 5 patients aged 22 to 27 who received cyclical treatment with Delpregnin for a period of 16 to 20 months. The cyclical changes in the vaginal epithelium were examined by means of serial observations In all 5 patients this was done during a control cycle before the treatment started during the first treatment-cycle and later on during every ... cycle. In 3 of the 5 patients vaginal films were also

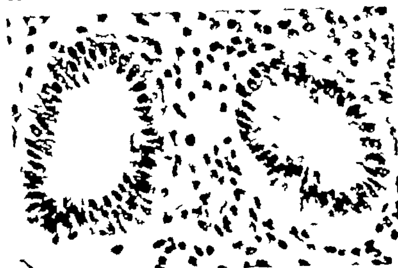


Fig. 3 Day 12. Increasing secretory activity. Both subnuclear and supranuclear vacuoles in the glandular epithelial cells.



Fig. 4 Day 14. Abortive secretory phase at its maximum with secretion in the glandular lumen and slight oedema of the stroma.

Figs. 1 to 6 Endometrial biopsies obtained during cyclical treatment with megestrol acetate+mestranol. (×400)

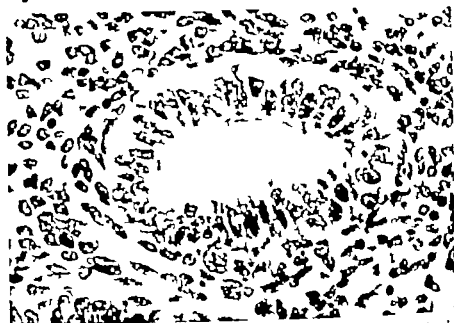


Fig. 1 Day 8. Early secretory activity Small subnuclear vacuoles in the glandular epithelial cells



Fig. 2 Day 10 Large subnuclear vacuoles in the glandular epithelial cells.

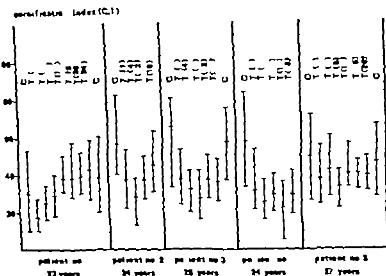


Fig. 7 Cornification Index (C.I.) range and mean in 5 fertile women before, during, and after cyclical treatment with megestrol acetate+mestranol. C= control cycle. T=treatment-cycle (the number in brackets indicates the duration of treatment in months)

to regress with narrowing of the lumen and decrease in the size of the cells. By days 24 to 25 the glandular cells become cuboidal and resemble those seen about day 5 of a normal cycle. Slight stromal oedema is seen about days 8 to 9. This oedema shows a tendency to increase up to about mid-cycle and then diminishes again, but it is never particularly pronounced. The stroma cell stimulation continues to be progressive throughout the cycle. From day 20 and until the onset of the withdrawal bleeding the stroma displays a moderate predecidual reaction.

Fig. 7 shows the C.I. range and mean for the 5 patients in the second group before, during and after treatment with Delpregnin. In the control cycles before treatment started there was some variation both in the level of cornification at each stage and in the degree of development of luteal pattern, but all patients showed a follicular phase leading to ovulation followed by a luteal phase. Futhermore there was fairly good correspond

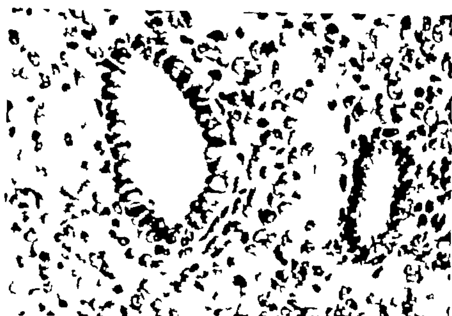


Fig. 5 Day 20 Regression of the glands.



Fig. 6. Day 24 Very small glands with cuboidal cells and abundant fibrillary stroma.

there is a slight to moderate predecidual reaction which is seen until the onset of the withdrawal bleeding

In this investigation we found that the endometrial changes during cyclical treatment with Delpregnin were independent of the numbers of treatment-cycles. Early secretory activity (subnuclear vacuoles) was seen as early as day 8. By days 12 to 13 the vacuoles became supranuclear in position before discharging secretion in the glandular lumen. The secretory activity reached a maximum on days 13 to 15 but the glands remained rather undeveloped. After this abortive secretory phase a regression of the glands was seen. The stroma showed slight oedema which was maximal in mid-cycle and from day 20 a moderate predecidual reaction was seen. This is in fairly good agreement with the findings of *Jackson* (1963) and *Roland et al* (1964)

Our results regarding the changes in the vaginal epithelium during cyclical treatment with Delpregnin confirm the findings of *Jackson* and *Linn* (1964) During treatment we found a moderate reduction in the range of C.I., and the mean decreased even in the first treatment-cycle. These changes in the C.I. were found during the whole treatment period, but as soon as the drug administration was stopped the range and the mean of C.I. reached pre-treatment levels. Of all the commonly used oral contraceptives—as mentioned by *Jackson* and *Linn* (1964)—the tablets containing a 17-hydroxyprogesterone derivative as gestagen seem to cause the smallest alteration in the vaginal smears as compared with pre-treatment levels

SUMMARY

This report describes the endometrial histology and the vaginal cytology during cyclical treatment with Delpregnin® (each tablet contains 5 mg of megestrol acetate + 0.1 mg of mestranol)

In the endometrium we found that the changes were almost independent of the number of treatment-cycles. Early secretory activity (subnuclear vacuoles) was seen as early as day 8 The secretion reached a maximum on days 13 to 15 but the glands remained rather undeveloped. This abortive secretory phase was followed by a regression of the glands. The stroma showed only

ence between the peak in C I and the rise in the basal body temperature indicating ovulation. Even during the first treatment-cycle the C.I was invariably reduced in range and the mean had decreased in all 5 patients. The smears showed considerable variability though the majority had a moderate C.I. and a moderate progesterone picture As shown in fig. 7 the range of C I. was reduced during the whole treatment period, and also the mean of C.I remained diminished during treatment in all patients except in patient no 1 In the control cycles immediately after cessation of medication the C.I. range and mean reached approximately the pre-treatment levels.

Discussion

Maqueo et al (1963) and *Rice-Wray et al.* (1963) have found that the endometrial response varies only very little from one gestagen to another depending on the dose and proportion of the gestagen in the tablet rather than its chemical composition. Furthermore they have found that after 3 cycles of treatment there is little further change in the endometrium These observations are not completely in agreement with those reported by *Jackson* (1963) who found that there are certain changes typical of various gestagen-oestrogen combinations which are so characteristic that one can usually tell which compound the woman is taking According to *Jackson* (1963) it is characteristic of the endometrium during cyclical treatment with an oral contraceptive containing a 17 hydroxyprogesterone derivative that the glands are usually quite well developed, the subnuclear vacuolization is rather pronounced, and the stroma is moderately oedematous with some predecidual reaction near the surface Certain patterns in the cyclical endometrial changes are however common to all main types of gestagens Even after a few days of treatment the endometrium is characterized by early secretory changes though with much less marked glandular development than normal and by the early appearance of basal vacuoles and more or less stromal oedema followed by glandular regression and abundant fibrillary stroma. Later in the cycle

e, Torben, Acta obst. et gynec. scandinav. 46, 428, 1967

om the Department of Surgery (A. Bindsler and B. Helberg, M.D.) and
e Department of Pathology (J. Ringsted and H. Hornbak, M.D.) the
olbaek County Hospital Holbaek Denmark

OVARIAN STROMAL HYPERPLASIA ASSOCIATED WITH HYPEROESTROGENISM IN A POST-MENOPAUSAL WOMAN

Report of a Case

BY

TORBEN BILDE

During recent years great interest has been shown in the ovarian stroma of post-menopausal women particularly when it shows hyperplasia. Several studies suggest that the cells of the ovarian stroma are able to produce oestrogens and hormonal function has been demonstrated in the ovary after the menopause (*Novak* 1953).

In 1956 *Wotiz et al.* demonstrated the *in vitro* conversion of testosterone to oestradiol and oestriol by ovarian tissue showing cortical stromal hyperplasia.

As far as we know no cases of hyperplasia of the cells of the ovarian stroma associated with hyperoestrogenism *in vivo* have been published. Consequently the following case may be of interest.

Case Report

Record No. 890716. A 78-year-old woman admitted because of metrorrhagia.

Previous history. Menarche at the age of 14. Menstruation was regular until the age of 47 (5–6 days/28 days). No vaginal discharge. Moderate dysmenorrhoea. Two normal deliveries, no abortions.

In 1936 (47 years old) admitted because of metrorrhagia, treated by curettage. Histological findings: hyperplasia of the endometrium.

In 1937 (48 years old) re-admitted because of metrorrhagia. Gynaecological examination showed nothing abnormal. Treatment: X-ray castration.

a slight oedema with a maximum in the mid-cycle. Moderate predecidual reaction was seen from day 20 to the onset of the withdrawal bleeding

In the vaginal epithelium we found a moderate reduction in the range of the cornification index (C.I) and a decrease in the mean of C I during the whole treatment period. These changes in the C.I ceased in the first post treatment cycle.

REFERENCES

de Allende I L. C. and *Orias O* Cytology of the Human Vagina. Hoeber New York, 1950

Durkin J W Jr Lin T J and *Kim Y J* Am. J Obst. & Gynec. *91* 110, 1965

Flowers C. E. Jr J.A.M.A. *188* 97 1964

Grant E. C G Conference of the Society for the Study of Fertility Oxford, July 1964 J Reprod. Fertil *8* 275 1964

Jackson M C. N and *Linn R* Int. J Fertil. *9* 75 1964

Jackson M C N Oliver Bird Lecture, 1963 *J* Reprod. Fertil. *6* 153, 1963

Larsen E Ugeskr Laeg. *126* 111 1964

Lin T J Durkin J W and *Kim Y J* Current Therap. Res. *6* 225, 1964

Maqueo M Perez Vega E. Goldzieher J W Martinez-Manautou J and *Rudel H* Am. J Obst. & *Gynec. 85 427 1963*

Maqueo M Becerra C Munguia H & *Goldzieher J W.*, Am J Obst. & Gynec. *90* 395 1964

Mears E In "Biological Council Symposium on Agents Affecting Fertility London *Churchill* p. *211 1965*

Pincus G Rock J and *Garcia C. R.* Ann. N Y Acad. Sci. *71* 677 1958

Pundel J P Les Frottis Vaginaux Endocriniens. Masson, Paris, 1952

Rico-Wray E Aranda-Rosell A. Maqueo M and *Goldzieher J W* Am. J Obst. & *Gynec. 87* 429 1963

Roland M Am. N Y Acad Sci *71* 638, 1958

Roland M Clyman M J Decker A. and *Ober W B.* Fertil and Steril. *15* 143 1964

Received on Sept. 29th, 1966

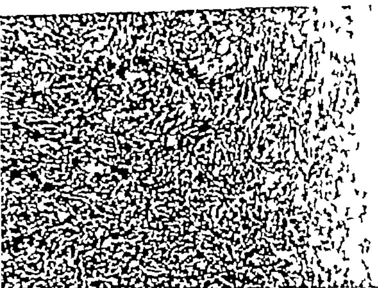


Fig 1 Ovarian cortical stromal hyperplasia (Micro. no 8977 H. and E.)

Macroscopic examination of the removed ovaries showed no tumours. Both ovaries were cut into 3 mm sections and all tissue was embedded in paraffin The microscopic examination also failed to show any tumour However the stroma of the ovarian cortex was found to be hyperplastic with relatively large cells with increased nuclear size and in pronounced whorl formation—a few cells had fairly abundant pale cytoplasm, but typical luteinization was not observed.

Examination of the uterus showed marked polypoid hyperplasia of the endometrium, and myomas In some areas, microscopic examination revealed characteristic Swiss-cheese pattern in the endometrium In other areas pronounced adenomatous hyperplasia was found, partly with an atypical gland picture including marked crowding of small glands with a pale-staining high columnar epithelium

Histological diagnosis

Ovaries hyperplasia of ovarian cortical stroma

Uterus cystic and adenomatous hyperplasia with anaplasia of endometrium, intramural myomas

At follow-up examination three months after discharge the patient complained of attacks of perspiration and hot flushes which were so pronounced that she had consulted her own doctor On physical examination nothing new was revealed.

In 1946 (57 years old) again admitted because of metrorrhagia. Gynaecological examination showed nothing abnormal. Treated by curettage. Histological findings hyperplasia of the endometrium.

In 1964 (75 years old) re-admitted because of metrorrhagia. She stated that since 1935 when she was 46 years old, she had had acyclical vaginal bleeding. The loss had sometimes been heavy but never with passage of blood clots. During the few years prior to admission, the haemorrhages had lasted for up to 3 weeks. Her own doctor had prescribed Vallestril tablets for a brief period, but the patient had taken only a few of the tablets. The patient had not taken any tablets for the 3 months before admission.

Physical examination revealed a well-preserved woman. No external signs of endocrine disease

Weight 74 kg. Height 161 cm. Blood pressure 140/90 mm Hg. Nothing abnormal was *found on physical examination.*

On gynaecological examination the vulva and vagina were found to be normal. A cervical polyp the size of a hazelnut was seen.

Recto-vaginal examination showed the uterus to be lying vertically. It was slightly enlarged, firm and mobile No pathological changes were palpable in the adnexa.

Curettage was performed and yielded an abundant quantity of tissue. *Histological findings* hyperplasia of the endometrium *indicating hormonal* influence; benign cervical polyp

Determination of the urinary excretion of oestrogens (biological method) showed a level of approximately 2400 mouse units (normal value after the menopause is approximately 20 mouse units)

Other investigations Hb 12.3 g per 100 ml. Serum-creatinine 1.1 mg per 100 ml. No albumin or sugar in the urine. Chest X-ray was normal. Intravenous pyelography showed no renal abnormalities, in *particular* no visible pathological changes were detected in the region of the adrenals.

The past history the histological report and the quantity of oestrogen found in the urine pointed to a hormone-producing tumour and therefore in addition to hysterectomy removal of both ovaries was indicated. Consequently total hysterectomy and bilateral salpingo-oophorectomy was performed.

At operation the ovaries were *found to be small but extremely vascular* The uterus was the size of a fist and slightly irregular due to small fibromas. During the operation the kidneys were examined. They were found to be smooth and well defined and, in particular the upper poles were normal.

The post-operative course was complicated by bronchopneumonia. The patient was discharged in good health 19 days after admission.

One month after the operation *the urinary excretion of* oestrogen was found to be approximately 20 mouse units. Determination of urinary gonadotrophin post-operatively showed a level of 200 mouse units (mean value for 74-year-old females 140, range 55-220)

found hyperplasia of the ovarian stromal cells in 72 per cent of 28 patients with breast cancer who were treated with oophorectomy However it is difficult to evaluate the importance of such statements, since other workers (*Marcus* 1963) have found that about one third of post-menopausal ovaries in a control series showed some cortical stromal hyperplasia.

Unfortunately hyperplasia of the cortical stroma is a rather poorly defined concept, based upon subjective morphological criteria which are difficult to evaluate quantitatively This may contribute to the uncertainty which prevails with regard to the endocrine influence of the hyperplastic ovarian stroma.

Some authors believe that the cause of ovarian hyperplasia occurring after the menopause should be sought for in the hypophysis. Thus, *Smith* (1955) suggests that the hyperplasia is a response to gonadotrophic stimulation. By examining 19 post menopausal women with hyperplasia of the ovarian stromal cells, *Burt* (1954) found a very high level of hypertrophic amphophils in the anterior lobe of the pituitary without any significant differences in other types of cells. Recent studies suggest that in post-menopausal women with hyperplasia of the ovarian stromal cells a universal endocrine disorder is the causative factor since a higher frequency of disorders such as diabetes and hypertension was found in these women than in a control series (*Novak* and *Mohler* 1947)

In the present case there is no doubt that the increased production of oestrogen took place in the ovarian stromal cells since the patient's excretion of oestrogen went down to minimum levels after oophorectomy Besides, the adrenal glands were found to be normal at the examination performed during the operation. On the other hand, physical examination did not reveal any signs of other endocrine disorders and the urinary gonadotrophin level was within normal limits.

SUMMARY

A case is reported of pronounced hyperoestrogenism with longstanding endometrial hyperplasia in a 78-year-old woman caused by ovarian cortical stromal hyperplasia.

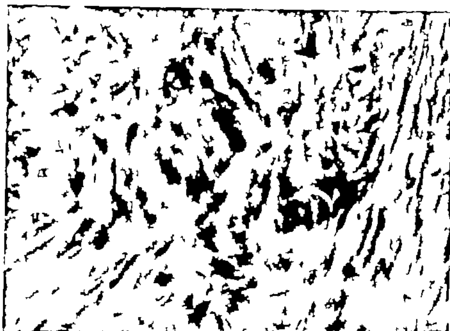


Fig. 2. Ovarian cortical stromal hyperplasia (Micro no. 6977 H. and E.)

Discussion

During the reproductive period the ovarian follicles produce most of the oestrogen in the body. This has been shown by studies of the content of the follicular fluid (*Smith* and *Smith*, 1946). It is known that oestrogen production also takes place outside the ovaries, in particular in the adrenal glands; however, under normal conditions this source is considered to be of secondary importance.

As early as in 1926 *Parkes* showed that the presence of follicles was not necessary for the synthesis of oestrogenic hormones in mice, as oestrus continued to appear after sterilizing irradiation. By contrast, the oestrus cycle stopped at once on removal of the ovaries. Examination of these ovaries did not reveal any follicles, but lipid-containing cortical cells.

Studies of the relationship between ovarian hyperplasia and types of cancer in the genesis of which oestrogens may play a part, suggest also that the production of oestrogens may occur in these stromal cells. Thus, in 1952 *McManus* and *Sommers*

Loeffler Frank, and Stearn, Roger Acta obst et gynec scandinav 46, 435, 1967
From the Department of Obstetrics and Gynaecology St. Luke's Hospital
Guildford Surrey England

ABDOMINAL HYSTERECTOMY WITH APPENDICECTOMY

BY

FRANK LOEFFLER AND ROGER STEARN

Introduction

The first recorded appendicetomy was incidental to a hernia repair (*Creese* 1953) It was carried out in 1734 by Claudius Amyard, Principal Surgeon to St. George's and Westminster Hospitals London, on a boy of 11 years with an inguinal hernia and scrotal fistula The hernial sac contained the appendix perforated by a pin. The appendix was removed and the hernia repaired but later it recurred. The pin was first sent to the Royal Society then to the British Museum and now it is lost. Since this operation, 230 years have elapsed and there is still controversy over the place of incidental appendicectomy particularly in obstetric and gynaecological surgery

Several American authors have advocated removal of the appendix at Caesarean section (*Larsson*, 1954 *Israel* and *Roitman* 1957 *Powell et al* 1958 *Speirs et al.*, 1959 *Sweeney* 1959 *Champion* and *Doolittle* 1961) and at post-partum sterilization (*Screier* and *Myers* 1960)

Many authors have advocated incidental appendicectomy in gynaecological surgery (*Goldspohn* 1913 *Smith* 1940 *Phillips*

Population Council F Bow, Department of Obstetrics and Gynaecology Akademiska Sjukhuset, Uppsala.
Senior Registrar Queen Charlotte & Chelsea Hospitals London, W 6
Consultant Obstetrician and Gynaecologist, Poole General Hospital, Dorset.

Acknou ledgement

Thanks are due to professor G Tellum M.D University of Copenhagen for valuable help with interpretation of histopathological findings.

REFERENCES

Burt A. S Cancer *7* 1227 1954
McManus R. G and *Sommers S C.* New Engl. J Med. *246* 890 1952
Marcus C. C Obst. & Gyn. *21* 175 1963
Novak E. R. and *Mohler D.*, Am. J Obst. & Gynec. *65* 1099 1953
Parkes A. S Proc. Royal Soc. London *100* 172, 1926
Smith G V Textbook of Endocrinology edit. 2, 1955
Smith O K and *Smith G V J* Clin. Endocrin. *6* 483 1946
Wotiz H H Davis J W Lemon H M and Gut M J. Biol. chem. 222 487 1956

Received on Aug. 12th 1966

Table I. Diagnosis on Discharge from Hospital

Diagnosis	Without Appendicectomy		With Appendicectomy	
Fibroids	203	49.7 %	64	43.5 %
Abnormal Bleeding	122	29.9 %	40	27.2 %
Fibroids and Endometriosis	23	5.6 %	11	7.5 %
Fibroids and Ovarian Tumor	13	3.2 %	7	4.8 %
Endometriosis	17	4.2 %	12	8.2 %
Others	30	7.4 %	13	8.9 %
Total	402	100.0 %	147	100.0 %

Table II. Distribution of Surgeons Performing Operations

Surgeon	Without Appendicectomy		With Appendicectomy	
Consultant I	55	13.5 %	68	46.3 %
Consultant II	180	44.1 %	25	17.0 %
Consultant III	23	5.6 %	0	0 %
Registrars	150	36.8 %	54	36.7 %
Total	408	100.0 %	147	100.0 %

Results

Mortality

There was only 1 death in the whole series giving an overall mortality of 0.18 er cent. The death occurred on the sixth post operative day in a patient who did not have the appendix removed and was thought to be due to broncho-pneumonia. A post-mortem examination was not held.

D ration of Stay in Hospital

Those patients who had the appendix removed spent an average of 13.8 days in hospital while the remainder stayed an average of 14.1 days.

1945 *Cianfrani* and *Zeigerman*, 1946 *Weir* 1948 *Taniguchi* and *Killenny*, 1950 *Pratt et al*, 1951 *Rosset* and *Conston*, 1951 *Powell et al* 1958 *Heller* 1959 *Wetterdal* 1962) Few have warned against it (*McDonald* 1939 *Marshall* and *Macer*, 1949 *Labry* and *Duroux*, 1951)

Howkins (1945) sent a questionnaire to 31 British surgeons Only 5 removed the appendix routinely 6 considered that they had seen complications as a result of incidental appendicectomy A few commented that appendicectomy undoubtedly increased the risk of post-operative pyrexia and infection and that it was a complicating factor in convalescence It was this statement that helped to prompt the present enquiry

Material Studied

From April 1955 to July 1960 555 total hysterectomies for non-malignant conditions were performed at St. Luke s Hospital, Guildford, Surrey England. In 147 cases (26.5 per cent) the appendix was removed in the remaining 408 (73 5 per cent) there was no incidental appendicectomy

In the 408 patients who did not have the appendix removed, 105 (25 7 per cent) had had a previous appendicectomy In 214 (52 4 per cent) the operation notes definitely stated that the appendix had been conserved In 23 patients (5 6 per cent) who had had a previous abdominal operation and 64 (15 7 per cent) others an account of the operative details did not include a description of the appendix

In both groups the ages of the patients ranged from 27 to 80 years the average being 45 4 years for those who had a hysterectomy alone and 45 9 years for those who had the appendix removed as well Table I shows that the diagnosis on discharge from hospital was similar in both groups. Table II shows that the type of operations performed by surgeons of consultant status varied in the two groups This is explained by the fact that only 1 of the 3 favoured routine appendicectomy In spite of this discrepancy the 2 groups seemed sufficiently similar in all but number to make a comparison of post-operative results valid All cases were nursed in the same ward.

Table I. Diagnosis on Discharge from Hospital

Diagnosis	Without Appendicectomy		With Appendicectomy	
Fibroids	203	49.7 %	64	43.5 %
Abnormal Bleeding	122	29.9 %	40	27.2 %
Fibroids and Endometriosis	23	5.6 %	11	7.5 %
Fibroids and Ovarian Tumor	13	3.2 %	7	4.8 %
Endometriosis	17	4.2 %	12	8.2 %
Others	30	7.4 %	13	8.9 %
Total	402	100.0 %	147	100.0 %

Table II. Distribution of Surgeons Performing Operations

Surgeon	Without Appendicectomy		With Appendicectomy	
Consultant I	55	13.5 %	68	46.3 %
Consultant II	180	44.1 %	25	17.0 %
Consultant III	23	5.6 %	0	0 %
Registrars	150	36.8 %	54	36.7 %
Total	408	100.0 %	147	100.0 %

Results

Mortality

There was only 1 death in the whole series giving an overall mortality of 0.18 er cent. The death occurred on the sixth post operative day in a patient who did not have the appendix removed and was thought to be due to broncho-pneumonia. A post-mortem examination was not held.

Duration of Stay in Hospital

Those patients who had the appendix removed spent an average of 13.8 days in hospital while the remainder stayed an average of 14.1 days.

Table III. *Temperatures*

	Without Appendicectomy		With Appendicectomy	
Febrile	166	45.6 %	53	36.1 %
Afebrile	198	48.5 %	88	59.8 %
No record	24	5.9 %	6	4.1 %
Total	408	100.0 %	147	100.0 %

Table IV *Antibiotics prescribed*

	Without Appendicectomy		With Appendicectomy	
Given antibiotics	120	29.4 %	45	30.6 %
No antibiotics	288	70.6 %	102	69.4 %
Total	408	100.0 %	147	100.0 %
Repeat course (%age of those treated)	11.1 %		9.1 %	

Morbidity

As a criterion of morbidity an elevation of temperature over 38.0 degrees Celsius on any day except that of operation, was regarded as abnormal Table III shows that 59.9 per cent of patients who had the appendix removed had an afebrile course of those with no additional surgery 48.5 per cent had an afebrile course In those patients with fever the temperature was elevated for an average of 2.58 days in those who had no appendicectomy while it was raised for a lower mean of 2.11 days in those who had it done Table IV shows that post operative antibiotics were similarly used in both groups.

Complications

The difference in the incidence of complications 33.3 per cent in those with appendicectomy as against 36.7 per cent in those without is insignificant. Table V gives an analysis of complica-

Table V Post-operative Complications

Complications	Without Appendicectomy		With Appendicectomy	
Recorded	136	33.3 %	54	36.7 %
None recorded	272	66.7 %	93	63.3 %
Urinary	54	12.4 %	26	17.6 %
Wound sepsis	46	11.3 %	16	10.9 %
Pelvic infection or haematoma	14	3.4 %	10	6.8 %
Wound dehiscence	5	1.2 %	1	0.7 %
Respiratory	24	5.9 %	6	4.1 %
Reactionary haemorrhage	4	1.0 %	1	0.7 %
Secondary haemorrhage	7	1.7 %	1	0.7 %
Ileus or obstruction	4	1.0 %	0	0 %
Venous	5	1.2 %	2	1.4 %
Pulmonary embolism	3	0.7 %	4	2.8 %

tions recorded. It is interesting to note than neither ileus nor intestinal obstruction occurred in patients who had had the appendix removed.

Discussion

The prevention of malignancy is one of the main reasons for prophylactic surgery. Carcinoid tumour is the only neoplasm found at all commonly in the appendix. *Warren* and *Warren* (1926) found an incidence of 0.38 per cent in 6,797 surgically removed appendices. However this tumour is rarely present in a macroscopically normal appendix.

Appendicectomy may be performed to guard against appendicitis in the early post-operative phase. In this series there were no recognised cases. *Howkins* and *Williams* (1963) record 1 case on the fifth day in a review of 1 000 hysterectomies. In an earlier communication, *Howkins* (1956) recalls 3 cases in which appendicitis occurred within a week of hysterectomy. This complication is undoubtedly very rare but because of difficulties in interpreting physical signs in the post-operative abdomen, could have serious consequences.

Incidental appendicectomy may be advocated as a means of avoiding subsequent laparotomy for removal of an inflamed or even a normal appendix. *Lee* (1961) calculated that in the National Health Service hospitals of England and Wales 7 000 to 8 000 women a year have unnecessary non incidental appendicectomies Routine removal of the appendix might reduce the incidence of these superfluous operations by eliminating the diagnosis which is often the main reason for surgery in a patient with abdominal symptoms and equivocal physical signs In this respect it is of course very important to make sure that a patient knows about an incidental appendicectomy *Salewski* (1955) even suggests a mock skin incision over McBurney s point as a method of avoiding confusion. In this series only 2 patients are known to have come to subsequent appendicectomy both at same time after leaving hospital.

A patient may request appendicetomy and this request may be dictated by a desire to avoid the discomfort or cost of a subsequent operation or by a phobia about developing appendicitis While a patient s wishes should always be taken into account they should not really influence a debate about the wisdom of prophylactic appendicectomy

An objection to prophylactic appendicectomy is the additional blood loss or operating time involved. Neither can be very significant where the procedure is easy Where the appendix is retro-caecal or bound down by adhesions these factors do assume greater importance Those who recommend that the appendix should only be removed if it shows signs of previous inflammation must appreciate that it is just this sort of incidental appendicectomy which may have disastrous results.

It might be argued that appendicectomy contributes to the risk of peritoneal contamination during hysterectomy but careful technique should minimise this possibility In this context it is worth mentioning the studies of *Desjacques* (1961) who took cultures from the meso-appendix in 100 cold appendicectomies and obtained intestinal flora in 36 per cent of cases. He uses this as an argument against prophylactic surgery It would be interesting to attempt to repeat this work.

Peritonitis ileus intestinal obstruction, haemorrhage or per-

foration of the appendix stump are the complications most feared by those who are against incidental appendicectomy. Any of these need occur only once to influence a surgeon's views more strongly than the most extensive statistical analyses. In this series none of these complications appeared nor was there any increase in other forms of morbidity following prophylactic surgery. The overall morbidity and mortality we record is comparable with that found by others (*Smith* 1940, *Jones* and *Doyle* 1943, *Weir* 1948, *Kimbell* 1950, *Pratt et al.* 1951, *Backer* and *Kristoffersen* 1957, *Schneider* and *Weed* 1958, *Howkins* and *Williams* 1963).

Conclusions

One must disagree with those who regard "incidental appendicectomy as a matter of duty" (*Goldspohn* 1913). Equally *Bonney's* (1952) description of appendicectomy as a "meddlesome chipping and chopping" is perhaps a little exaggerated, particularly as he previously states that he is prepared to remove the appendix if the patient requests it.

Lahey (1953) strikes a balance in saying "I would like to urge that the decision for or against removal of the appendix in any patient operated on for a lesion distant from the appendix should always err in the direction of not doing it unless it can be done with complete ease, with adequate exposure and without undue manipulation."

With these precautions and provisos there would seem to us to be no harm in this form of prophylaxis, particularly as this series shows no evidence that it increases the morbidity, complications or mortality associated with abdominal hysterectomy.

SUMMARY

1) A comparative analysis has been made of 147 hysterectomies with incidental appendicectomy and 408 hysterectomies without removal of the appendix.
2) The added procedure did not influence the morbidity or mortality in this series of cases.

Incidental appendicectomy may be advocated as a means of avoiding subsequent laparotomy for removal of an inflamed or even a normal appendix. *Lee* (1961) calculated that in the National Health Service hospitals of England and Wales 7 000 to 8 000 women a year have unnecessary non-incidental appendicectomies Routine removal of the appendix might reduce the incidence of these superfluous operations by eliminating the diagnosis which is often the main reason for surgery in a patient with abdominal symptoms and equivocal physical signs. In this respect it is of course very important to make sure that a patient knows about an incidental appendicectomy *Salewski* (1955) even suggests a mock skin incision over McBurney's point as a method of avoiding confusion. In this series only 2 patients are known to have come to subsequent appendicectomy both at same time after leaving hospital

A patient may request appendicetomy and this request may be dictated by a desire to avoid the discomfort or cost of a subsequent operation or by a phobia about developing appendicitis While a patient's wishes should always be taken into account they should not really influence a debate about the wisdom of prophylactic appendicectomy

An objection to prophylactic appendicectomy is the additional blood loss or operating time involved. Neither can be very significant where the procedure is easy Where the appendix is retro-caecal or bound down by adhesions these factors do assume greater importance Those who recommend that the appendix should only be removed if it shows signs of previous inflammation must appreciate that it is just this sort of incidental appendicectomy which may have disastrous results.

It might be argued that appendicectomy contributes to the risk of peritoneal contamination during hysterectomy but careful technique should minimise this possibility In this context it is worth mentioning the studies of *Desjacques* (1961) who took cultures from the meso-appendix in 100 cold appendicectomies and obtained intestinal flora in 36 per cent of cases. He uses this as an argument against prophylactic surgery It would be interesting to attempt to repeat this work.

Peritonitis ileus intestinal obstruction haemorrhage or per-

Taniguchi T and Kilkenny G S. Amer J Obstet. Gynec. 60 1359 1950
Warren S. and *Warren A. S* Ann. Surg. 83 222, 1926
Weir W C., Amer J Obstet. Gynec. 56 1151 1948
Wetterdal, P Svensk Läkartid. 59(1) 336 1962

Received on Sept. 2nd, 1968

Acknowledgements

We are grateful to Miss W D Grantham, Mr S S F Pooley and Mr Ewart Williams for their encouragement and allowing us to use their cases and also to Professor Peter Huntingford for his help and criticism in the presentation of this paper

REFERENCES

Backer O G and *Kristoffersen* K Acta chir scand. *114* 67 1957
Bonney V A Textbook of Gynaecological Surgery 6 ed. p. 70 London. Cassell 1952
Champion P K and *Doolittle* J E Obstet. Gynec. *18* 200 1961
Cianfrani T and *Ziegerman* J H Amer J Obstet. Gynec. *51* 109 1946
Creese P G Surg. Gynec. Obstet. *97* 643 1953
Desjacques M R Mem. Acad. Chir *87* 851 1961
Goldspohn A Amer J Obstet. *67* 481 1913
Heller E F Brun. Beitr Klin. Chir *199* 80 1959
Howkins J Lancet (i) 1016 1956
Howkins J and *Williams* D J Obstet. Gynaec. Brit. Cwlth. *70* 20 1963
Israel S L and *Roitman* H B Obstet. Gynec. *10* 102, 1957
Jones H O and *Doyle* L W Amer J Obstet. Gynec. *46* 160 1943
Kimbell C W Proc. R. Soc. Med. 53 969 1950
Labry R and *Duroux* P E Lyon Chir *46* 889 1951
Larsson E J Amer med. Ass *154* 549 1954
Lahey F H Lahey Clin. Bull. 8 98 1953
Lee J A H Lancet (ii) 815 1961
Marshall H K and *Macer* G West. J Surg. 57 365 1949
McDonald E P N Y State J Med. 39(*i*) 503 1939
Phillips J H Amer J Obstet. Gynec 50 174 1945
Powell D V *Holmes* D E *Beath* D H *Yard* G H and *Noel* P J Obst. Gyn., N Y *12(6)* 727 1958
Pratt J H *Lee* M J *Hassbarl* W F and *Brandes* R W Amer J Obstet. Gynec. *64* 407 1951
Rosset E M and *Couston* A S Amer J Obstet. Gynec *61* 1136, 1951
Salewski H D Zentralbl. Chir 80 699 1955
Schneider G T and *Weed* J C Southern Med. J *51* 561 1958
Screier P C and *Myers* J D Southern Med. J 53 539 1960
Smith P H Amer J Obstet. Gynec *40* 118 1940
Speirs R E *Baum* A H *Williams* E R and *Boles* R D Ann. Surg. *25* 958 1959
Sweeney W J Obstet. Gynec. N Y *14* 588 1959

Bonte J.T.P. and Verbrugge H.P. Acta obst. et gynec. scandinav. 46, 445, 1967

From the Department of Health Development (Professor J. H. de Haas) of the Netherlands Institute for Preventive Medicine TNO–Leiden

MATERNAL MORTALITY

An Epidemiological Approach

BY

J. T. P. BONTE AND H. P. VERBRUGGE

1. *Introduction*

Research on maternal mortality tends more toward the clinical than the epidemiological approach. In this publication an epidemiological approach is pursued, emphasizing comparisons according to age in an international context.

The low frequency of clinical confinements in the Netherlands (30 per cent) makes it possible to compare the results with those of countries with high hospitalization.

The similarity between perinatal (and infant) mortality in the Netherlands and Sweden and the great difference in hospitalization at confinement are a strong stimulus to pay special attention to the comparison of maternal mortality in both these countries, which evolve at different levels.

2. *Statistical presentation*

Operational definitions in vital statistics focus on notification, registration and calculation, but vary in detail from country to country. Therefore special attention is given to the Dutch procedures.

2.1 Notification and registration

Notification of death and therefore of a case of maternal mortality is compulsory. The doctor who diagnoses death, fills out a death certificate (drawn up according to international agreements) also in cases attended by midwives.

The notification is sent to the CBS (Central Bureau of Statistics—The Hague) without the intervention of other authorities. The returns may be incomplete sometimes because the doctor lacks sufficient information. Pregnancy may be unknown in women dying during the first months

Bonte, L.T.P. and Verbrugge, H.P. Acta obst. et gynec. scandinav. 46, 445, 1967
From the Department of Health Development (Professor J. H. de Haas) of the Netherlands Institute for Preventive Medicine TNO–Leiden

MATERNAL MORTALITY

An Epidemiological Approach

BY

L.T.P. BONTE AND H.P. VERBRUGGE

1. *Introduction*

Research on maternal mortality tends more toward the clinical than the epidemiological approach. In this publication an epidemiological approach is pursued, emphasizing comparisons according to age in an international context.

The low frequency of clinical confinements in the Netherlands (30 per cent) makes it possible to compare the results with those of countries with high hospitalization.

The similarity between perinatal (and infant) mortality in the Netherlands and Sweden and the great difference in hospitalization at confinement are a strong stimulus to pay special attention to the comparison of maternal mortality in both these countries which evolve at different levels.

2. Statistical *presentation*

Operational definitions in [illegible] tal statistics focus on notification, registration and calculation, but vary in detail from country to country. Therefore special [illegible]ttention is given to the Dutch procedures.

2.1 Notification and [illegible]egistration

Notification of death and therefore of a case of maternal mortality is compulsory. The doctor who diagnoses death, fills out a death certificate (drawn up according to international agreements) also in cases [illegible]ttended by midwives.

The notification is sent to the CBS (Central Bureau of Statistics—The Hague) without the intervention of other authorities. The returns may be incomplete sometimes because the doctor lacks sufficient information. Pregnancy may be unknown in [illegible] woman dying during the first months of [illegible]

gestation. In the case of women dying a considerable time after delivery the relation between death and pregnancy parturition and puerperium may not be realized.

For *registration* the CBS adheres to international definitions (par. 22) and rules for classification of WHO WHO sets no time limit for the complications of puerperium. The CBS limits this period to one year post partum. This limit was repeatedly altered before 1950 By these inaccuracies comparability—in time and internationally—is scarcely affected, as the number of women dying a long time after delivery amount to only a fraction of total maternal deaths.

The primary cause of death is classified according to the three lists of the International Statistical Classification of Diseases Injuries and Causes of Death (I.C.D) the list of three-digit categories (Detailed List) List A (Intermediate List of 150 Causes) and List B (Abbreviated List of 50 Causes) The place of death (at home or in hospital) is only given in List B.

The detailed list records the number of cases in which a given cause of death has been notified as a primary or as a secondary cause. It is impossible to deduce possible connections between primary and secondary causes of death from these data.

During the five years 1960–1964 the number of secondary causes of death in maternal mortality comprised 40 per cent (196) of the number of primary causes of death (436) The CBS booked half the secondary causes of death (60 in 5 years) under no. 649 pregnancy associated with other conditions. The number of pregnant women dying from other conditions (accidents, common diseases) must certainly be higher but the number is unknown since this information is not requested on the death certificate.

Of the other half of the secondary causes of death *four fifths* were also booked primarily under maternal mortality but under a different item. In the case of women dying from haemorrhage resulting from solutio placentae, the *haemorrhage may be booked as the primary the toxaemia as a secondary* cause of death. The remaining one f fth, or 10 per cent of the secondary causes of death comprise causes not booked under maternal mortality e.g. *carcinoma, mitral stenosis, etc.*

Although the death certificate asks for the parity of the deceased mother this information is not always given (par 2.3)

2.2 *Definition and omenclature*

According to the I.C.D all women dying from complications of pregnancy (640–649) delivery (670–678) and puerperium (680–689) and as a result of delivery without complications (660) and abortion (650–652) should be booked under maternal mortality (640–689) This classification makes it possible to differentiate deaths according to obstetrical period. *During the* years under consideration no deaths were booked under no. 660.

The I.C.D gives the following definition of the components of maternal mortality·

The complications of delivery refer to full-term and premature deliveries of live- and stillbirths. They exclude dead foetuses of less than approximately 7 months or 28 weeks gestation (p. 195)

Abortion includes premature confinement with a dead foetus of less than approximately 7 months or 28 weeks gestation (p 193)

In the Netherlands since 1950 stillbirth refers to pregnancies of more than 28 weeks duration instead of 26 weeks before 1950

The A-list gives classification—according to age—into six main diagnostic groups sepsis (115) toxaemia (116) haemorrhage (117) abortion without mention of sepsis or toxaemia (118) abortion with sepsis (119) other complications (120)

According to the A-list haemorrhage comprises loss of blood from placenta praevia, solutio placentae, retentio placentae, etc. Loss of blood occurring in ectopic pregnancies rupture of the uterus etc. are booked under the rest-group A 120 As result this rest-group comprises both causes of death with a clearly defined diagnoses and vaguely delineated causes of death In most countries an important part (40 %) of maternal mortality is booked under A 120 43 % in Sweden and the Netherlands with Norway (27 %) and France (45 %) as extremes

The B-list states no more than total maternal mortality (B 40) In the Netherlands divided into tw groups

B 40a—puerperal infection and septicaemia

b—other complications of pregnancy childbirth and puerperium

Only the B-list indicates the place of death (home or hospital) B 40a does not cover sepsis of pregnancy and is therefore less complete than sepsis of the A-list (115–117)

2 3 Calculation

The maternal mortality rate is more difficult to determine accurately than is the case in other causes of death

In determining the denominator of maternal mortality choice must be made on practical grounds of one out of several quantities the number of deliveries, births (live- stillbirths) or live-births

The ideal denominator the number of conceptions—is never known. This makes an assessment of the fatality-risk of pregnancies- abortions and deliveries impossible

The number of deliveries, as a whole or according to maternal age, is hardly ever published For international comparisons the number of live born infants has to be employed as the only available—and dependable—denominator This denominator is in fact used by WHO (UN Handbook of Vital S tistics Methods p 189 and 190) A better approximation of the fatality-risk can be achieved by adding the still-births to the live-births in the denominator but the (age-specific) stillbirth rate which varies according to time and country is usually not (accurately) known

In spite of these limitations the concept of maternal mortality has been employed successfully in medical statistics, even in an international context. For the comparison between Sweden and the Netherlands the total number of births can be applied in calculating maternal mortality

In this publication rates have been calculated for two- and three-year periods and analysis according to causes has been given for five-year periods, as annual figures, especially for age-specific data in small countries are liable to fluctuations. An exception has been made for the last two years (1964 and 1965) which show a different pattern.

For international comparisons two three-year periods were considered, 1950/1952 and 1960/1962. The interval of 10 years was chosen, as maternal mortality was halved during this period in Western European countries and as the age at birth has shown considerable change After our analysis was completed WHO published the data of 1963 They have been inserted in table 3

Changing birth-patterns and the influence of age on maternal mortality both in a given country in the course of time and in different countries during the same time make it impossible to compare crude rates directly For this reason rates have been adjusted to the distribution of age at birth. *As the age-specific rates are calculated from a small number of deaths* indirect standardization has been applied.

The adjusted rate (AR) has been calculated as follows $AR = CR \times \frac{SR}{ER}$ in which CR = crude rate of the population to be standardized, SR = (crude) death rate in standard population ER = expected death rate. $ER = \frac{\Sigma(p \times sr)}{P}$

in which sr = age-specific rates of the standard population, p and P the number of births respectively per age-group and total $(P = \Sigma p)$ of the *population to be standardized*

For international comparisons over the period 1960/1962, England and Wales were chosen as the standard population for the following reasons: (a) dependable registration (b) large population, resulting in practically no annual fluctuations in the age-specific rates (c) non-extreme distribution of age at birth, (d) mortality rates in the same order as the Netherlands and Scandinavia.

In order to discover the true fall in maternal mortality standardization should not be confined to age but include both age and parity However *standardization according* to parity is impractible as information on parity is seldom available. Only British studies (Confidential Enquiries) mention age and parity making it possible to calculate that the influence of age exceeds by far that of parity Standardization according to age approaches 80 per cent of the combined influence of age and parity

3 *Trend in the Netherlands*

At the beginning of the twentieth century maternal mortality

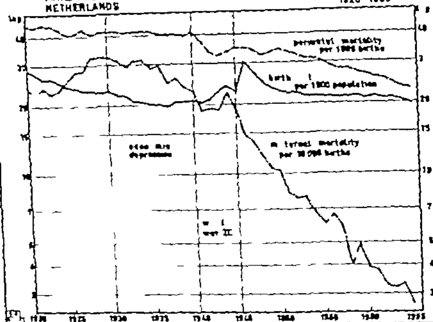


Fig 1

fluctuated around the 20–25 per 10 000 births. Remarkably enough a rise occurred after 1925 reaching 34 per 10 000 in 1928/1930 after which a fall set in. The level of the beginning of the century was not reached again until 1940. After the second world war the falling tendency was enhanced maternal mortality being halved between 1946 and 1956 (from 14.9 to 6.7 per 10 000) and halved again between 1956 and 1963/1964 (from 6.7 to 3.3 per 10,000). Maternal mortality has been decimated since 1935.

Both in 1963 and 1964 82 mothers died from causes directly related to pregnancy and childbirth 3 1/4 per 10 000 births. The decrease has not yet come to a standstill. In 1965 maternal mortality dropped below 3 per 10 000 (that is 66 mothers) and in 1966 a crude rate of 2 per 10 000 was reached.

Maternal mortality and perinatal mortality are both so intimately related to parturition that a correlation seems probable.

Up to 1940 perinatal mortality decreased slowly from 45 per 1000 in 1920 to 41 per 1000 in 1940 This fall continued at an increasing rate in and after the second world war (with the exception of the period 1944/1945) reaching 25 per 1000 in 1963 Both perinatal mortality (notably stillbirth) and maternal mortality show an increasing fall after the second world war be it at different speeds.

The maternal mortality level was high from 1925 to 1940 while the birth rate fell from 25 to 21 per 1000 population. During the post war birth peak maternal mortality was decreasing sharply and continued to fall in the fifties while the birth rate was nearly constant There appears to be no correlation between birth rate and maternal mortality

No explanation was found in the Dutch literature for the rise in maternal mortality from 23 to 33 per 10 000 births between 1924 and 1928 and the horizontal course until 1935 The rise cannot be explained by changes in nomenclature of causes of death. These were introduced in 1921 and 1929 Over the period 1920–1955 maternal mortality decreased to the same extent as total mortality for women in the 15–44 age-group. For this reason the proportion of total mortality accounted for by maternal mortality during this period remained practically unchanged—7.5 per cent—with the exception of the thirties when it rose to 11 per cent This proportion gradually fell to below 5 % during the sixties

4 *Maternal mortality by age*

4 1 *The Netherlands*

Table I, showing the age-distribution of mothers since 1936/1937 was compiled in order to investigate the influence of age at childbirth on the trend of maternal mortality This demonstrates that while before 1950 age-distribution changed little after that date a trend towards younger childbirth set in. This means that a differentiation according to age is mandatory for the evalua-

Table I. *Births by Age of Mother. Percentage Distribution. Netherlands 1936–1965*

period	<20	20–24	25–29	30–34	35–39	40–44	≥45	total
1936/1937	2	17	30	27	17	7	1	100
1940/1942		1	30	26	17	6	1	100
1950/1952	2	17	31	28	17	7	1	100
1955/1957	2	18	32	28	15	6	1	100
1960/1962	3	21	33	24	14	5	0	100
1963/1965	4	24	33	22	12	4	0	100

Table II. *Maternal Mortality by Age. Rates and Indices. Netherlands 1936–1965*

period	20	20–24	25–29	30–34	35–39	40–44	≥45	all ages crude	all ages adjusted[1]
				per 10,000 births					
1936/1937	12.1	16.2	19.0	24.6	40.8	65.7	136.9	27.3	27.3
1940/1942	13.3	12.4	13.7	20.9	29.8	46.6	53.8	20.4	20.5
1950/1952	8.7	4.9	5.2	7.5	14.4	21.8	45.2	8.7	8.7
1955/1957	(1.2)	3.9	3.5	5.4	10.7	17.6	55.7	6.2	6.4
1960/1962	(1.6)	2.0	2.0	3.2	7.4	13.8	(17.5)	3.6	4.0
1963/1965	(1.2)	1.5	1.6	3.5	7.2	9.9	(20.8)	3.1	3.5
				indices 1950/1952 100					
1936/1937	139	331	365	328	283	301	303	313	314
1940/1942	153	253	263	279	207	214	119	233	236
1950/1952	100	100	100	100	100	100	100	100	100
1955/1957	(14)	80	67	72	74	81	123	71	74
1960/1962	(18)	41	38	43	51	63	(39)	42	46
1963/1965	(14)	31	31	47	50	45	(46)	36	40

( ) number of deaths 5 ,

[1] adjusted to birth distribution of 1950/1952

Table II and Figure 2 show that maternal mortality (except perhaps in the case of very young mothers) increases with age th effect becoming more noticeable with lower rates.

In the under 30 age-group maternal mortality in 1963/1965 amounted to no more than 1½ per 10.000 Over 30 mortality

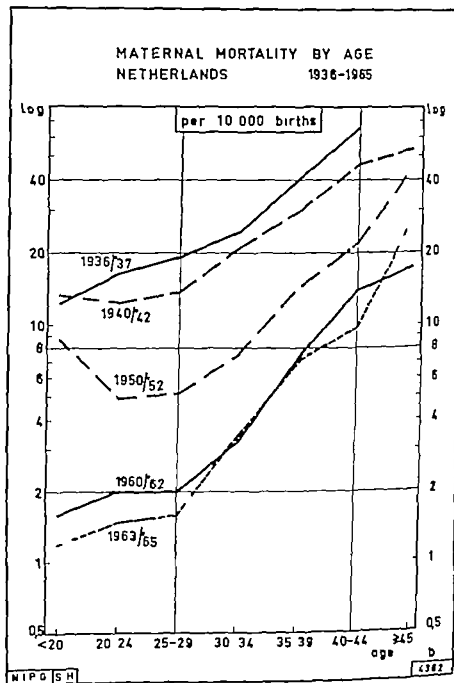

MATERNAL MORTALITY BY AGE
NETHERLANDS 1936-1965
per 10 000 births
log
40
20
10
8
6
4
2
1
0,5
1936/37
1940/42
1950/52
1960/62
1963/65
<20
20 24
25-29
30 34
35 39
40-44
≥45
age
NIPG SH
4382

Fig. 2.

rises steeply reaching 10 per 10 000 in 40–44 year old mothers. Mortality above 45 years of age is over 20 per 10 000 but has little influence on total maternal mortality on account of the small number of births (< ½ per cent) involved.

The drop in maternal mortality has occurred in all age-groups, but not evenly During a quarter of a century maternal mortality has been decimated in women under 30 and has decreased to one sixth for mothers over 30 (maternal mortality below 30 years has shown a greater fall than over 30) In 1936/1937 maternal mortality between 35–39 was 2.5 times that between 20–24 In 1965 almost five times Since 1960/1962 there has been little (or no) decrease in maternal mortality for women over 30 years.

According to Figure 3 in 1963/1965 61 % of all births and 31 % of all maternal mortality occurred in women of under 30 years, these percentages being 22 and 26 for 30–34 years, 12 and 28 for 35–39 years and 4 and 16 % for the over 40 years age-group respectively The over 35 year age-group comprises only 16 per cent of all births but 44 % (almost half) of all maternal deaths.

Indirect standardization (par 2.3) of maternal mortality in 1963/1965 to the Dutch birth distribution of 1950/1952 resulted in a rate of 3 5 per 10,000 instead of the crude rate of 3 1 (Table II) The gross fall amounts to 5.6 per 10 000 (8 7–3 1 per 10 000) and after standardization for age, 5.2 per 10 000 (8 7 3.5 per 10 000) The difference—0 4 per 10 000 or 7 per cent of the total decrease—is caused by a shift to lower ages at childbirth. This shift becomes more and more important, being responsible for one fifth of the decrease between 1963/1964 and 1965

4 2 *International comparison*

The preceding paragraph has demonstrated that the level of maternal mortality is determined to an important degree by maternal age Standardization for age at childbirth is therefore necessary in international comparison.

Table III. *Maternal Mortality in Specified Countries. Crude and Adjusted Rates 1960/1962 & 1963 Compared with Hospitalization and Birth Rate*

Country	Maternal mortality per 100,000 live births				Hospitalization 1962 %	Birth rate 1962 %
	1960/1962		1963			
	crude	adj.	crude	adj.		
Sweden	23.6	23.6	26.6	26.9	100	14.[illegible]
Denmark	24.3	26.0	25.5	27.5	50	16.6
Norway	30.0	27.1	20.5	18.9	96	17.2
Belgium	36.3	34.7	30.8	28.7	90	16.9
England & Wales	36.3	36.3	28.5	28.5	66	17.5
U.S.A. total	36.4	39.0	35.8	38.1	97	23.1
white	24				99	22.1
nonwhite	96*				87	31.4
Netherlands	37.0	31.5	32.8	27.8	30	20.9
Czechoslovakia	43.8	50.3	36.0	41.2	96	15.8
France	46.7	44.4	38.2	35.5		17.7
West Germany	96.9	94.1	82.8	79.5	77	17.8

adjusted to birth distribution of England & Wales
in percent of all deliveries
1962/1963
1961

4 2.1 *Crude and adjusted rates*

Table III gives a review of the crude and adjusted rates for various countries together with hospitalization and birth rates. According to the crude rates of 1960/1962 the eleven countries can be divided into four groups of which the first group (Sweden and Denmark) has a maternal mortality of under 25 per 100 000 the second group (Norway) around 30 the third (Belgium, England and Wales, USA and the Netherlands) 36–37 and the fourth group 40 per 100 000 Maternal mortality in West Germany was over 95 per 100 000

In 1963 the situation has changed, the rates of most countries showing a (remarkable) decrease The three Scandinavian countries having similar rates may be considered as one group. Together they have about as many births as the Netherlands. The rates of all countries of the third group except U.S.A. have

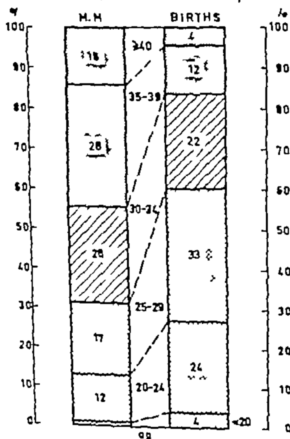

MATERNAL MORTALITY AND BIRTHS
BY AGE OF MOTHER
percentage distribution
NETHERLANDS
1963/1965
M.M
BIRTHS
100
90
80
70
60
50
40
30
20
10
0
≥40
35-39
30-34
25-29
20-24
<20
16
28
28
17
12
4
12
22
33
24
4

Fig 3

become much lower The same holds true for the fourth group maternal mortality in Czechoslovakia and France has fallen under 40 per 100 000 The crude rate of West Germany decreased less than in other countries and still is 80 per 100 000 births.

After standardization to age at birth (par 2.3) the order changes. This applies specifically to the Netherlands which "raises" to the second place (immediately behind the Scandinavian countries) although its maternal age pattern is still "backward in Western Europe in spite of a trend towards younger childbirth.

In 1960/1962 the crude rates of maternal mortality in the Netherlands are 50 per cent higher than in Scandinavia in 1963 30 % and the adjusted rates 25 % and 12 % respectively

In 1963 the range between countries with a high and low adjusted rate has become smaller The Netherlands are closely followed by Belgium and England and Wales. Maternal mortality in France has become lower than in U.S.A.

4 2.2 *Trend*

When building up a picture of maternal mortality in various countries comparisons may not be limited to present rates (after standardization) but an analysis of the trends should also be undertaken.

On practical grounds—similar crude maternal mortality rates available data, varying age at birth—five countries from Table III are suitable for mutual comparison over the periods 1950/1952 and 1960/1962 England and Wales, France Sweden, USA and the Netherlands.

Table IV gives a summary of the age at birth in these five countries and shows a shift in the age at birth to younger age-groups with the exception of France, where remarkable enough *no change* in maternal age occurred during the fifties. The USA is at the other extreme the low age at birth continues to fall, so that at the present half of all parturients are less than 25 years old. England and Sweden have practically the same age distribution over both periods with a relatively high number of young mothers 32 % under 25 years in 1950/1952 and almost 40 per cent in 1960/1962. Compared to other countries the Netherlands

Table IV *Live Births in Specified Countries by Age of Mother Percentage Distribution, 1950/1952 & 1960/1962*

country	period	< 20	20–24	25–29	30–34	35–39	40–44	≥ 45	all ages
Engl & Wales	A	4	28	32	21	11	3	0	100
	B	7	31	31	19	10	3	0	100
France	A	4	30	33	18	10	4	0	100
	B	4	28	33	21	11	3	0	100
Sweden	A	7	25	29	22	12	4	0	100
	B	10	29	28	19	10	3	0	100
U.S.A.	A	12	32	29	17	8	2	0	100
	B	14	34	25	16	8	2	0	100
Netherlands	A	2	17	32	26	17	7	1	100
	B	3	21	33	24	14	5	0	100

A 1950/1952 B = 1960/1962

has few young mothers (19 per cent under 25 years in 1950/1952 and 25 per cent in 1960/1962) and many older mothers, 25 and 19 per cent respectively over 35 years, but the fall in maternal age is relatively strong.

In accordance with this shift the influence of the lowering age at birth on maternal mortality during a decade is strongest in the Netherlands and England and weakest in France 6 and 1 per cent respectively of the total decrease while in Sweden and the USA these percentages are 4 and 1 ½ per cent respectively

Table V shows the age-specific and total maternal mortality (crude and adjusted) of these five countries over two periods. In 1950/1952 maternal mortality in England, France, the USA and the Netherlands stood at the same level (around 80 per 100 000) Until 1962 three of these four countries show a fall to around 36 per 100 000 France only to 47 Maternal mortality in Sweden, which was around 70 fell most (to 24 per 100 000) The range (of the crude rates) between the above mentioned countries has increased.

Maternal mortality increases with age independently of period, country or level of rates.

become much lower The same holds true for the fourth group maternal mortality in Czechoslovakia and France has fallen under 40 per 100 000 The crude rate of West Germany decreased less than in other countries and still is 80 per 100 000 births.

After standardization to age at birth (par 2.3) the order changes This applies specifically to the Netherlands which raises to the second place (immediately behind the Scandinavian countries) although its maternal age pattern is still "backward in Western Europe in spite of a trend towards younger childbirth.

In 1960/1962 the crude rates of maternal mortality in the Netherlands are 50 per cent higher than in Scandinavia, in 1963 30 % and the adjusted rates 25 % and 12 % respectively

In 1963 the range between countries with a high and low adjusted rate has become smaller The Netherlands are closely followed by Belgium and England and Wales. Maternal mortality in France has become lower than in U.S.A.

4 2.2 *Trend*

When building up a picture of maternal mortality in various countries comparisons may not be limited to present rates (after standardization) but an analysis of the trends should also be undertaken

On practical grounds—similar crude maternal mortality rates, available data varying age at birth—five countries from Table III are suitable for mutual comparison over the periods 1950/1952 and 1960/1962 England and Wales France Sweden, USA and the Netherlands.

Table IV gives a summary of the age at birth in these five countries and shows a shift in the age at birth to younger age-groups with the exception of France where remarkable enough no change in maternal age occurred during the fifties The USA is at the other extreme the low age at birth continues to fall, so that at the present half of all parturients are less than 25 years old. England and Sweden have practically the same age distribution over both periods with a relatively high number of young mothers 32 % under 25 years in 1950/1952 and almost 40 per cent in 1960/1962. Compared to other countries the Netherlands

Table IV Live Births in Specified Countries by Age of Mother Percentage Distribution. 1950/1952 & 1960/1962

country	period	<20	20–24	25–29	30–34	35–39	40–44	≥45	all ages
Engl & Wales	A	4	26	32	21	11	3	0	100
	B	7	31	31	19	10	3	0	100
France	A	4	30	33	18	10	4	0	100
	B	4	28	33	21	11	3	0	100
Sweden	A	7	25	29	22	12	4	0	100
	B	10	29	29	19	10	3	0	100
U.S.A.	A	12	32	29	17	8	2	0	100
	B	14	34	25	16	8	2	0	100
Netherlands	A	2	17	32	26	17	7	1	100
	B	3	21	33	24	14	5	0	100

A 1950/1952 B = 1960/1962

has few young mothers (19 per cent under 25 years in 1950/1952 and 25 per cent in 1960/1962) and many older mothers 25 and 19 per cent respectively over 35 years but the fall in maternal age is relatively strong.

In accordance with this shift the influence of the lowering age at birth on maternal mortality during a decade is strongest in the Netherlands and England and weakest in France 6 and 1 per cent respectively of the total decrease while in Sweden and the USA these percentages are 4 and 1 ½ per cent respectively

Table V shows the age-specific and total maternal mortality (crude and adjusted) of these five countries over two periods. In 1950/1952 maternal mortality in England, France the USA and the Netherlands stood at the same level (around 80 per 100,000) Until 1962 three of these four countries show a fall to around 36 per 100 000 France only to 47 Maternal mortality in Sweden, which was around 70 fell most (to 24 per 100 000) The range (of the crude rates) between the above mentioned countries has increased.

Maternal mortality increases with age independently of period, country or level of rates.

Table V *Maternal Mortality in Specified Countries by Age Rates[1] and Indices 1950/1952 & 1960/1962*

Country	period	<20	20–24	25–29	30–34	35–39	40–44	≥45	all ages crude	all ages adj
Engl. & Wales	A	47	44	59	86	170	254	1281	82	
	B	20	22	25	46	80	143	145	36	39
	I	42	50	43	53	47	56	11	44	47
France	A	49	49	60	85	176	234	456	81	
	B	25	23	30	58	107	165	383	47	47
	I	52	47	51	68	61	71	84	58	58
Sweden	A	64	39	43	71	139	215	278	69	
	B	(12)	12	12	28	66	109	(314)	24	25
	I	(19)	31	29	39	47	51	(113)	34	37
U.S.A.	A	62	44	58	96	166	280	756	75	
	B	21	19	30	55	88	136	245	36	37
	I	34	44	51	58	53	49	49	48	49
Netherlands	A	89	50	52	77	148	227	481	89	
	B	(16)	20	20	33	75	142	183	37	40
	I	(18)	40	39	43	51	63	38	42	45

A = rates 1950/1952 per 100 000 live births
B = rates 1960/1962 adjusted to birth distribution of 1950/1952
I = indices 1950/1952 = 100 ( ) = numbers of deaths ≤ 5

As the decrease in maternal mortality is more pronounced for younger than older age-groups and a shift to younger age-groups takes place the influence of age gradually increases as shown for the Netherlands in par 4 1

During the 1950/1952 period mortality for women over 35 was around five times as high as for mothers under 25 in 1960/1962 seven times

Maternal mortality under 20 was higher than from 20–25 during the 1950/1952 period. In England and the Netherlands maternal mortality for the under twenties has fallen below that of the 20–24 age-group A similar tendency is visible in other countries

5 Sweden—Netherlands

The favourable perinatal and infant mortality situation, both in Sweden and the Netherlands the similar socio-hygienic circumstances and the difference in the percentage of hospital confinements (Sweden 100 per cent, the Netherlands 30 per cent) necessitate a comparison of maternal mortality in these two countries.

5 1 *Trend*

Figure 4 illustrates the trend of the crude and adjusted rates in the two countries since 1950 and Figure 5 the trend of the age-specific rates.

During the 1951/1952 period the crude rates of maternal mortality in Sweden and the Netherlands were respectively 71 and 79 per 100 000 births in 1962/1964 20 and 33 and in 1965 14 and 27 per 100 000 After standardization—to the birth-distribution in Sweden 1951/1952—the difference between Swedish and Dutch mortality becomes smaller In 1951/1952 the adjusted rates for Sweden and the Netherlands are equal (70 per 100 000) In 1962/1964 the difference (after standardization) amounts to 10 per 100 000 Both in 1956/1958 and in 1962/1964 the adjusted rates are 50 per cent higher in the Netherlands than in Sweden, but this difference relates to low rates. The lag of the Netherlands behind Sweden develops after 1951 and increases up to 1958 Afterwards the decrease in Sweden fell off and both curves are now running parallel. In 1965 both countries show a remarkable fall in Sweden still more than in the Netherlands.

The decrease in Holland in 1965, most probably continuing in 1966, emanates from the reduction in the under 30 year age-group and the steep fall of the main cause haemorrhage (par 5 2)

The equal adjusted mortality rates in Sweden and the Netherlands during the 1951/1952 period were the resultant of three components equal mortality for mothers over 40 a slightly higher mortality in Sweden for women from 30–40 years and a lower mortality under 30 (Fig. 5) In both countries the mortality

Table V *Maternal Mortality in Specified Countries by Age Rates and Indices 1950/1952 & 1960/1962*

Country	period	<20	20–24	25–29	30–34	35–39	40–44	≥45	all ages crude	all ages adj
Engl. & Wales	A	47	44	59	86	170	254	1281	82	
	B	20	22	25	46	80	143	145	36	39
	I	42	50	43	53	47	56	11	44	47
France	A	49	49	60	85	176	234	456	81	
	B	25	23	30	58	107	165	383	47	47
	I	52	47	51	68	61	71	84	58	58
Sweden	A	64	39	43	71	139	215	278	69	
	B	(12)	12	12	28	66	109	(314)	24	25
	I	(19)	31	29	39	47	51	(113)	34	37
U.S.A	A	62	44	58	96	166	290	756	75	
	B	21	19	30	55	88	136	745	36	37
	I	34	44	51	58	53	49	49	48	49
Netherlands	A	89	50	52	77	148	227	481	89	
	B	(16)	20	20	33	75	142	183	37	40
	I	(18)	40	39	43	51	63	38	42	45

A = rates 1950/1952 per 100,000 live births
B = rates 1960/1962 adjusted to birth distribution of 1950/1952
I = indices 1950/1952 = 100 ( ) = numbers of deaths ≤5

As the decrease in maternal mortality is more pronounced for younger than older age-groups and a shift to younger age-groups takes place the influence of age gradually increases as shown for the Netherlands in par 4 1

During the 1950/1952 period mortality for women over 35 was around five times as high as for mothers under 25 in 1960/1962 seven times

Maternal mortality under 20 was higher than from 20–25 during the 1950/1952 period In England and the Netherlands maternal mortality for the under twenties has fallen below that of the 20–24 age-group A similar tendency is visible in other countries.

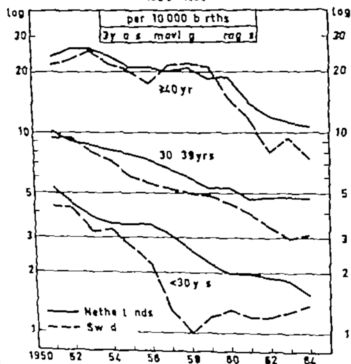

MATERNAL MORTALITY
SWEDEN AND NETHERLANDS
BY AGE
1950–1965
log
per 10 000 births
≥40 yr
30 39yrs
<30 y s
Netherlands
Sweden
1950 52 54 56 58 60 62 64

Fig 5.

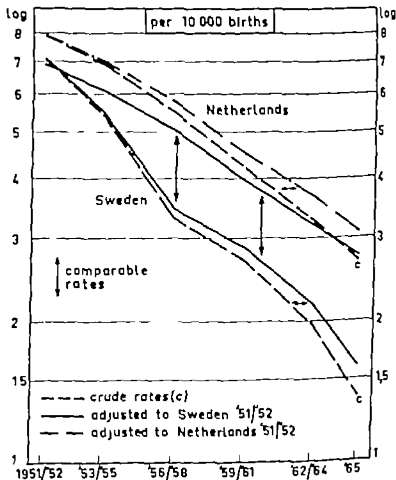

MATERNAL MORTALITY
SWEDEN AND NETHERLANDS
crude and adjusted rates
1951–1965
per 10 000 births
log
8
7
6
5
4
3
2
1,5
1
Netherlands
Sweden
comparable rates
c
crude rates (c)
adjusted to Sweden '51/'52
adjusted to Netherlands '51/'52
1951/52
'53/55
'56/58
'59/61
'62/64
'65
NIPG
SH

Fig. 4

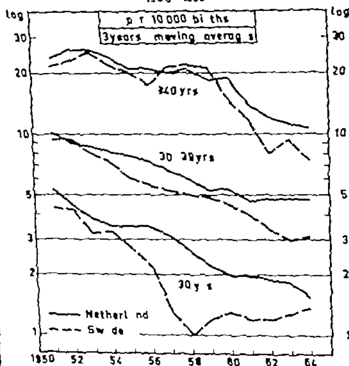

MATERNAL MORTALITY
SWEDEN AND NETHERLANDS
BY AGE
1950–1965
log
p r 10 000 bi ths
3years moving averag s
30
20
10
5
3
2
1
log
30
20
10
5
3
2
1
40 yrs
30 39yrs
30 y s
Netherl nd
Sw de
1950
52
54
56
58
60
62
64

Fig. 5

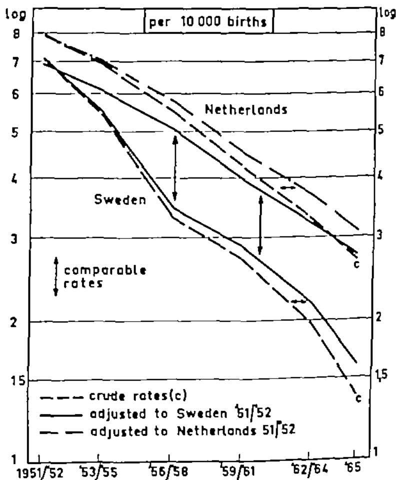

MATERNAL MORTALITY
SWEDEN AND NETHERLANDS
crude and adjusted rates
1951–1965
per 10 000 births
log
8
7
6
5
4
3
2
1,5
1
Netherlands
Sweden
comparable rates
c
crude rates(c)
adjusted to Sweden '51/'52
adjusted to Netherlands 51/'52
1951/52
'53/'55
'56/'58
'59/'61
'62/'64
'65
NIPG
SH
4360

Fig. 4

Table VI. *Maternal Mortality by Cause Per 100,000 births. Sweden & Netherlands 1951 1965*

no. list A	Cause	Sweden			Netherlands		
		1951/55	1959/63	1964/65	1951/55	1959/63	1964/65
115	sepsis	4.7	(0.9)	–	10.1	5.5	5.8
116	toxaemia	20.6	8.4	5.6	13.4	5.5	4.6
117	haemorrhage	8.3	3.0	(1.6)	17.7	9.2	5.4
118	abortion with sepsis	4.2	2.0	(2.0)	3.0	1.8	(1.0)
119	abortion without sepsis	1.4		(0.4)	1.5	0.8	(0.4)
120	other	21.9	9.7	6.9	27.1	15.2	10.5
	total	61.1	23.9	16.5	72.8	38.0	29.6

( ) number of deaths ≤ 5 —— highest rates

both countries (60 per cent) for other causes the decrease was greater in Sweden than in the Netherlands.

After 1963 in Sweden toxaemia, haemorrhage and other causes continued to fall and in the Netherlands haemorrhage and other causes show a sharp decrease from 9.2 to 5.4 and from 15.2 to 10.5 per 100 000 respectively

While keeping in mind the restrictions discussed in par 2.2 concerning the rest group A 120 it may be stated that until 1963 in Sweden toxaemia was the main cause of death and in the Netherlands haemorrhage. At present toxaemia is equally important in both countries (around 6 per 100 000) and haemorrhage has lost its dominant position in the Netherlands.

Abortion is not a prominent cause of mortality in either country Because of the decrease of haemorrhage and toxaemia in the Netherlands these two causes have reached the same level as sepsis This component of maternal mortality did not decrease

in Sweden sepsis is insignificant. The fall in the rest group A 120 is only a little less rapid in both countries than that of maternal mortality as a whole.

While the age-specific rates for total maternal mortality have been illustrated in Figure 4 age-specific and age-adjusted rates by

rates of these three age-groups are decreasing Mortality in mothers over 40 fell equally rapidly in both countries until ± 1960, after this Sweden had a slight lead. From 1951 mortality of mothers between 30 and 40 fell gradually in both countries, in Sweden more than in the Netherlands Since 1960/1962 in the Netherlands the decrease is leveling-off for women over 30 years (par 4 1) In the last years in Sweden the same tendency occurs. Maternal mortality in the under 30 year age-group in the Netherlands fell gradually from 49 per 100 000 in 1951/1952 to 15 in 1964/1965 In Sweden the fall was equally rapid from 1951/1952 until 1954/1955 (from 45 to 33 per 100 000) and subsequently more rapid, but during the last few years the trend has been towards a leveling-off at a figure of 13–14 per 100 000 in 1964/1965 In the Netherlands the trend is still towards a further decrease

The divergence in the adjusted rates of Sweden and the Netherlands up to 1956/1958 is mainly accounted for by the difference in decrease for women under thirty The combined effects of the three age components has resulted in an equal rate of fall in both countries after 1956/1958

Total maternal mortality will further decrease if the older age-groups become relatively less important, even if the rate in the younger age-groups (under 30 years) shows no substantial fall.

5 2 *Causes of death*

An analysis of causes (of death) is necessary for a comparison of maternal mortality between Sweden and the Netherlands. In this context also only a relative meaning can be assigned to the concept of cause (of death)

Table VI shows the crude rates of the main causes of maternal mortality for the Netherlands and Sweden during the periods 1951/1955 and 1959/1963, differentiated according to the intermediate list of causes of death (List A) Thanks to recent data it has now been possible to add the two-year period 1964/1965 During the last years a drastic change has taken place

Until 1963 maternal mortality had been (more than) halved for all groups of causes The decrease in toxaemia was equal in

Table VIII. *Maternal Mortality by Cause. Percentage Distribution. Sweden & Netherlands 1951 1965*

no. list A	Cause	Sweden			Netherlands		
		1951/55	1959/63	1964/65	1951/55	1959/63	1964/65
115	sepsis	7.7	3 9	–	13.9	14 6	19.5
116	toxaemia	33 7	34 9	34.1	18 4	14 4	22.1
117	haemorrhage	13 6	12 4	9 8	24.3	24 3	18.1
118	abortion with sepsis	6 8	8.5	12.2	4 1	4.7	3 4
119	abortion without sepsis	2 4		2.4	2 1	2.1	1.3
120	other	35 8	40 3	41 5	37.2	40 0	35 6
	total	100	100	100	100	100	100

Table IX. *Maternal Mortality by Obstetrical Period. Rates and Percentage Distribution. Sweden & Netherlands 1959–1965*

Complications by obstetrical period	Per 100 000 Births				Percentage Distribution			
	Sweden		Netherlands		Sweden		Netherlands	
	59/63	64/65	59/63	64/65	59/63	64/65	59/63	64/65
abortion	3 2	2.4	2 6	1 4	13	15	7	5
pregnancy	8 9	6 4	9 7	9 5	37	39	26	32
delivery	9 5	6 4	16 9	8 9	40	39	44	30
puerperium	2 4	(1 2)	8 9	9 7	10	7	23	33
total	23 9	16 5	38 0	29 6	100	100	100	100

( ) number of deaths 5

relatively large group in both countries about 40 per cent of total maternal mortality Other countries show the same picture.

Table IX gives a classification of maternal mortality—both rates and percentage distribution—by obstetrical period. pregnancy delivery and puerperium. During the last few years an important change has taken place in the Netherlands

The complications of delivery and puerperium were far more common as causes of death in the Netherlands than in Sweden

Table VII *Maternal Mortality by Age and Cause Crude and Adjusted Rates per 100,000 births. Sweden & Netherlands 1959–1963*

no. list A	Cause	< 30		30–34		35–39		≥ 40		all ages		
										crude		adj
		S	N	S	N	S	N	S	N	S	N	S
115	sepsis	(0.3)	3.4	(2.0)	7 0	(3 8)	8.2	–	15.9	(0.9)	5.5	1.0
116	toxaemia	6.2	3.5	10 0	4 3	11 4	9.9	35.6	20 7	8.4	5.5	9 6
117	haemorrhage	(1 1)	4 4	(4 0)	7 0	(7 6)	19 8	(23.7)	46.2	3.0	9.2	3 6
118 119	abortion	(1 1)	1 4	(3 0)	4.3	(3.8)	(2.9)	(11.9)	(6.4)	2 0	2.6	2 3
120	other	4.9	7.9	14.0	13 7	22.9	34 4	47.5	52.5	9 7	15.2	11.4
	total	13.5	20.6	33.1	36 4	49.3	75.2	118.6	141 7	23.9	38 0	27.8

S = Sweden adjusted to age at birth in the Netherlands
N = Netherlands ( ) number of deaths ≤ 5

cause may be found in Table VII In both countries the rates for the various groups of causes show a steep rise with increasing age specifically in the case of toxaemia and even more so in that of haemorrhage. After (indirect) standardization of the Swedish rates to the age at birth in the Netherlands, Swedish rates for all causes of death rise

In Table VII most of the Swedish rates have been put between brackets as the number of deaths per group amounts to less than 5 However in Sweden also the age-specific pattern of causes of death is so consistent that the rate placed in brackets are of value in their mutual relationship

Table VIII shows that until 1963 in Sweden one third of the cases of maternal mortality were registered under toxaemia (A 116) against one sixth in the Netherlands. On the other hand haemorrhage (A 117) was responsible for a quarter of Dutch and one eighth of Swedish maternal mortality

During the last few years sepsis, toxaemia and haemorrhage each contribute about 20 per cent to total maternal mortality in the Netherlands In Sweden toxaemia kept its dominant place

The causes of death registered under A 120 comprise a

The Netherlands show that relatively good results can be achieved with a low percentage (30 per cent) of hospital confinements. Within the Netherlands, as in international comparisons, no direct connection is found between the level of hospitalization and maternal mortality. In rural areas with only 20 % hospitalization maternal mortality stands at the same level as in the big towns (>100 000 inhabitants) with 45 per cent hospitalization.

Compulsory health insurance comprises three quarters of all pregnant women and offers pre-natal care and obstetrical aid by family doctor or midwife free of charge. The ratio of doctor to midwife is 2 1 in the country as against 1 2 in towns. Opportunities exist for referral to a regional hospital—and therefore to an obstetrician—if complications threaten. These provisions together with 20–40 per cent hospitalization, relatively favourable socio-hygienic circumstances and small distances from hospitals appear to be sufficient to achieve a relatively low maternal mortality at least in "healthy" women, with an average height of 166 cm, having an increase of 3 cm over the last decade

Since 1956 the B-list in the Netherlands indicates place of death —hospital or home—by cause of death. This differentiation has formed the basis for Table X, which shows that three quarters of all maternal deaths occur in hospitals This ratio has remained practically unchanged from 1956–1964 During this period maternal mortality was more than halved in hospitals and nearly halved at home, from 178 to 78 and 22 to 13 per 100,000 respectively The fall in mortality was regular in hospitals, but initially steep in home deliveries stagnating later (at a lower rate) In 1965 again a steep decline of maternal mortality in home deliveries took place, bringing down the rate to only 6 per 100 000 Hospitalization has only slightly increased as in the previous years

Table X shows that the decrease of total maternal mortality in 1965 originates for two thirds (13 out of 17 deaths) from home deliveries. The level of mortality in hospitals remains bout ten times as high as in home deliveries owing to the cumulation of pathological cases.

complications of delivery being almost twice (respectively 17 and 9 5 per 100 000) and complications of puerperium four times (respectively 9 and 2.5 per 100 000) as frequent

In the Netherlands complications of delivery have been (more than) halved during the last few years parallel with the sharp decline of haemorrhage as a cause of death. Complications of puerperium went up a little In Sweden the rates for all causes decreased by one third. Complications of pregnancy and delivery have reached equal levels (6 4 per 100 000) The rates of complications of pregnancy and abortion fell by 1 per 100 000 births in the Netherlands Around 1960 complications of delivery and puerperium were much higher in the Netherlands than in Sweden, at present complications of puerperium form the essential difference in maternal mortality between the two countries.

6 *Hospitalization and maternal mortality*

In view of the exceptional position occupied by the Netherlands in comparison to the other Western European countries by its low rate of hospital confinements maternal mortality must be analysed according to place of confinement and place of death. The comparison of maternal mortality in Sweden and the Netherlands may give an answer to the question whether the percentage of deliveries taking place in maternity homes or hospitals (hospitalization) shows a direct relationship to the level of maternal mortality

Table III shows both crude and adjusted rates of maternal mortality and the percentage of hospital confinements in specified countries. It can be seen that Sweden has the lowest maternal mortality and the highest hospitalization (100 per cent) Mutatis mutandis the same applies for Norway (96 per cent) But USA, Belgium and Czechoslovakia with 90 per cent or more hospitalization have a higher maternal mortality than the Netherlands

All countries have over 50–60 per cent hospitalization, but a maternal mortality which is either higher or lower than the Netherlands. West Germany occupies a special position with 70 per cent hospitalization and a very high maternal mortality (in 1963 still 83 per 100 000)

Table XI *Maternal Mortality by Cause and Place of Death, Netherlands* B40 *and b* 1956–1963

Period	Hospital		Home		Total	
		b		b	a	b
			absolute numbers			
1956–1959	33	356	7	117	40	473
1960–1963	20	249	14	67	34	316
			per 100,000 births			
1956–1959	13.1	141.1	1.0	16.5	4.2	49.2
1960–1963	6.9	85.8	2.0	9.5	3.4	31.7
			percentage distribution			
1956–1959	11	89	6	94	8	92
1960–1963	7	93	17	83	10	90

sepsis
b all other causes } B40

A special study has demonstrated that in home deliveries maternal mortality is very low especially in the maternity home help group In the Netherlands the organization for maternity home help exists which sends simply trained (young) women to families where they assist the doctor or midwife at the delivery provide nursing care for mother and child and run the household during ten days post partum. This organization lends its assistance in half the home deliveries (approaching 100 000 deliveries per year) Home deliveries with maternity home help always had a maternal mortality below the already low average for home deliveries. In this connection it is probably of importance that the maternity home help continually observes the mother before and after childbirth and warns the doctor or midwif on the suspicion of abnormalities.

7 *Discussion*

In industrialised countries maternal mortality is of relatively small importance as a cause of death within total mortality

Table X. *Maternal Mortality by Place of Death. Netherlands 1950-1965*

Period	Hospital			Home			Total			Hospitalization[1] %
	n	r	i	n	r	i	n	r	i	
1950/1951	–	–	–	–	–	–	216	93	150	19 9
1956/1957	108	178	100	39	22.2	100	147	62	100	25.7
1958/1959	86	132	74	23	12.9	58	109	45	73	26 8
1960/1961	74	106	60	20	11.3	51	94	38	61	28 2
1962/1963	61	81	46	21	11 6	52	82	32	52	30 0
1964	60	78	44	23	13 0	59	83	33	53	30 4
1965	56	72	40[2]	10	5.8[2]	26[2]	66	27	44	31 5[2]

n = number of deaths
r = rate per *100*,000 births
i = index rate 1956/1957 = 100

in % of all births
estimated

When complications arise or threaten in home deliveries the patient is usually taken to hospital These urgent cases may have a relatively high maternal mortality and add to maternal mortality in hospitals while lowering maternal mortality in home deliveries. This mechanism does not explain the sudden decrease of maternal mortality in home deliveries in 1965

If maternal mortality was to be differentiated according to place of booking the rate for hospitals would fall with a consequent rise for home deliveries It is however impossible to verify this as the place of booking is not registered.

The relatively low maternal mortality in the Netherlands may not be allowed to obscure the fact that sharp and timely selection of high risk groups—for hospitalization—will produce a further reduction of maternal mortality More strongly the same applies to perinatal mortality as was pointed out previously in a study on perinatal mortality in the Netherlands (1962)

In the Netherlands B 40 is split up into two groups B 40a sepsis and B 40b other causes (par 2.2) In the Netherlands too sepsis as a cause of death continues to diminish especially in hospitals (Table XI) No great reduction can be expected in the sepsis mortality in home deliveries the present rate being only 1–2 per 100 000

Table XI *Maternal Mortality by Cause and Place of Death. Netherlands* B40 and b 1956–1963

Period	Hospital		Home		Total	
		b	a	b		b
			absolute numbers			
1956–1959	33	356	7	117	40	473
1960–1963	20	249	14	67	34	316
			per 100,000 births			
1956–1959	13.1	141.1	1.0	16.5	4.2	49.2
1960–1963	6.9	85.8	0	9.5	3.4	31.7
			percentage distribution			
1956–1959	11	89	6	94	8	92
1960–1963	7	93	17	83	10	90

a sepsis
b all other causes } B40

A special study has demonstrated that in home deliveries maternal mortality is very low especially in the maternity home help group In the Netherlands the organization for maternity home help exists which sends simply trained (young) women to families where they assist the doctor or midwife at the delivery provide nursing care for mother and child and run the household during ten days post partum. This organization lends its assistance in half the home deliveries (approaching 100 000 deliveries per year) Home deliveries with maternity home help always had a maternal mortality below the already low average for home deliveries. In this connection it is probably of importance that the maternity home help continually observes the mother before and after childbirth and warns the doctor or midwif on the suspicion of abnormalities.

7 *Discussion*

In industrialised countries maternal mortality is of relatively small importance as a cause of death within total mortality

amounting to 5 % in women of the 15–45 age-group (after 1950) It is however often the object of detailed analysis, because of among other things the tragical and sudden character of maternal deaths

These studies may be divided into two groups

a epidemiological analysis of national or regional data
b clinical the medico-obstetrical case studies

Epidemiological publications are based on population data and causes of death statistics They indicate trends over extensive periods sometimes together with a brief international comparison of crude mortality rates. The numbers with which these investigations are concerned are greater than those of clinical studies but owing to the limited amount of data in mortality statistics, statistical studies admit of only limited conclusions. Biological factors like age and parity have rarely or never been analysed in international comparisons

Medico-obstetrical analysis makes detailed studies of individual fatalities but is usually limited to small or selected groups. The "Reports on confidential enquiries into maternal deaths in England and Wales occupy a special place in the literature also in connection with age and parity

The object of these British and other studies is the ascertainment of preventible (avoidable) factors which have contributed to death. Criteria are not always well delineated and sometimes incomparable This lack causes a large scatter in the percentage of avoidable deaths (30–80 per cent) The decision whether patient midwife doctor or hospital were at fault is subject to a wide range of opinion in various publications There is a striking similarity in these studies in so far that haemorrhage (in the widest sense) is stated to be the most important cause of death. This cause of death also comprises the largest percentage of preventible factors. Comparison of investigations is difficult owing to vague criteria different composition of diagnostic groups the varying periods during which the investigations took place and lack of data about the group of women concerned. All studies of maternal mortality conclude that further reduction is possible in spite of sometimes already low rates.

In our analysis the influence of age on maternal mortality was stressed, as mortality rises with age. Specifically maternal mortality over 30 is much higher than under 30 years.

This age-specific influence means that a shift in the age at childbirth to younger age-groups will result in a passive fall in maternal mortality

In comparisons involving different periods and/or countries standardization for age (and if possible also for parity) is necessary as birth patterns in all countries are shifting towards younger mothers and may differ considerably among various industrialized countries at any given period.

In industrialized countries with low and decreasing maternal mortality and continuing shifts in birth patterns it is not justified to use crude rates for international comparison. As the Netherlands occupy a favourable position with regard to perinatal and infant mortality it might be expected that the same would apply for maternal mortality When measured by crude rates this is not the case but after standardization for age the Netherlands follow immediately behind the Scandinavian countries.

The sudden decrease of maternal mortality in the Netherlands —from 3 3 to 2.7 per 10 000—over the last few years (continuing in 1966) is closely bound up with the following interrelated factors a remarkable decrease in mortality from haemorrhage, the further decrease of maternal mortality under the age of 30 and increase in the shift to lower age at birth and last but not least a steep fall in maternal mortality in home deliveries.

When considering whether further improvement would be possible the country with practically the lowest maternal (and perinatal) mortality—Sweden—should be compared to the Netherlands The difference in mortality between these countries still amounts to (after standardization) 1 per 10 000. Compared with Sweden a reduction of 25 maternal deaths annually could be reached in the Netherlands.

The difference between the Netherlands and Sweden could be practically completely explained—after differentiation according to obstetrical period—by a higher mortality from complications of delivery and puerperium in the Netherlands. At present complications of puerperium form the essential difference This agrees

with the comparison according to causes of death, where sepsis and haemorrhage durante partu and post-partum, specifically in the over 35 age-groups occupy a much more important place in the Netherlands than in Sweden, while the rates for toxaemia approach each other

As the rates for all causes rise steeply with age—at most haemorrhage followed by other causes (A 120 partly haemorrhage) toxaemia, sepsis and abortion—timely hospitalization of mothers over 35 in the Netherlands will result in a further decrease of maternal mortality A sharper selection of mothers under 35 years belonging to high-risk groups will have the same effect

The pattern of perinatal mortality especially of stillbirth, shows a close similarity to that of maternal mortality both in regard to the trend and the increase in mortality with increasing maternal age and parity (with the exception of the first parity) Measures for the prevention of maternal mortality will also exert a favourable effect on perinatal mortality and vice versa

A further fall in maternal mortality may be expected in the Netherlands on better selection of the high-risk groups timely hospitalization of these groups and further improvement of treatment

SUMMARY

This study presents an epidemiological approach to maternal mortality on the basis of available national and international data. Special attention is paid to the comparison Sweden—the Netherlands.

Accent has been laid especially in view of international comparisons on definitions notification, registration and calculation. The importance of age-specific mortality rates has been stressed.

In the Netherlands maternal mortality has been decimated since 1935 The post war fall has been torrential In 1966 maternal mortality became under 2 per 10 000 births.

Since maternal mortality of the under twenties has fallen below that of the 20–24 age-group maternal mortality increases with age and increasingly so as rates are lower After standardization

by age the Netherlands rank immediately behind the Scandinavian countries, while on crude rates it would take the seventh place in international comparison.

The adjusted rates of Sweden and the Netherlands were equal in 1951/1952 and diverged until 1956/1958 Thereafter the fall runs parallel.

Apart from the restgroup A 120 haemorrhage is the most important cause of maternal mortality in the Netherlands against toxaemia in Sweden. In both countries the rates for the various groups of causes show a steep rise with increasing age. The difference between Sweden and the Netherlands could practically be explained by the different incidence in complications of delivery and puerperium. At present complications of puerperium form the essential difference.

Neither internationally nor in the Netherlands can a direct correlation be demonstrated between maternal mortality and a high percentage of deliveries in maternity homes and hospitals

Acknowledgements

We wish to express our gratitude to the staff of the Central Bureau of Statistics in The Hague for their valuable co-operation.

We are most grateful to Dr A. M. Bolander of the Central Bureau of Statistics in Stockholm for providing us with the recent Swedish data.

Translation has been performed by M. van Blankensteyn, M D

REFERENCES

Alison F Rev Hyg Med soc 10 677 1962

Alison F and Mme Corone Bull Inst nat Hyg Paris, 17 443 1962

Bjerre B and Arndt B Acta obst et gynec scandinav 43 1 1964

Cannell D E Maternal mortality New York Harper 1963 (Clinical Obstetrics and Gynecology Series, Vol 6, nr 4)

Central Bureau of Statistics, Mth Bull Vit Hlth Stat The Hague 12 17 1964

Committee on Maternal and Child Care of the Council on Medical Service of the American Medical Association Guide for maternal death studies with causes of obstetric deaths, direct and indirect, and reports on a study of seven programs Chicago, 1957

Dietel H and Kräling G., Münch med Wschr 106 57 1964

Fox L P Amer J Obstet Gynec 83 1504 1962

Froewis J and *Senker F* Wien. klin. Wschr 72 925 1960
Green G H N.Z. med. J 65 80 1966
Haas J H de Perinatal mortality and maternity home help in the Nether-lands Neonatal Studies 3 71 1954
Haas-Posthuma J H de Perinatal mortality in the Netherlands; an in-vestigation into factors influencing perinatal mortality Leiden, 1962
Janssens J., T soc. Geneesk. 43 657 1965
Kaser O Dtsch. Gesundh. Wes. 16 378, 1961
Klaus K Dtsch. Gesundh. Wes. 16 374 1961
Lane R. E. and *Andelman S L.* Amer J Obstet. Gynec. 85 61 1963
Mackenzie M. R. Ned. T Verlosk. 63 425 1963 (d)
Ministry of Health, Reports on confidential enquiries into maternal deaths in England and Wales 1952–1954 1955–1957 1958–1960 1961 1963, London HMSO (Reports on public health and medical subjects nrs 97 103 108 115)
O Driscoll K. and *Meagher D* J Obstet. Gynaec. Brit. Cwlth 69 249 1962
Rom F de and *Tirms A.* Bull. Féd. Soc. Gynéc. Obstét. franç. 11 144, 1959
Rom F de Rom R. de et *Petit M* Bull. Féd. Soc. Gynéc. Obstét. franç. 11 157 1959
Schockaert J A. Het Kind 41 445 1966 (d)
Sindram I S Ned. T Geneesk. 94 1555 1950 (d)
– Ned. T Verlosk. 51 128 1951 (d)
Sjövall A. Dtsch. Gesundh. Wes. 16 380 1961
Symposium on maternal mortality Amer J Obstet. Gynec. 83 1495 1962
Sendi B und *Lakatos I* Fortbild. 55 973 1961
Verbrugge H P T soc. Geneesk. 43 315 1965 (d)
Wesselink D G Ned. T Geneesk. 5 1555 1931 (d)
National Reports on Vital and Health Statistics
Belgium, Czechoslovakia, Denmark, England and Wales France Nether-lands, Norway Sweden, U.S.A., West Germany
United Nations Demographic Yearbooks
World Health Organization – Epidem. vital Statist. Report 16 633, 1963
– World health statistics annual
– Epidemiological and vital statistics reports

(d) = publication in Dutch

Received on Jan. 23rd, 1967

Kuhlbäck, B., Widholm, O., Skrifvars, B., Nieminen, U., Pasternack, A., Tallgren, L., and von Knorring, J. Acta obst. et gynec. scandinav. 46, 475, 1967

From the Renal Ward, Fourth Department of Medicine (Professor Bertel von Bonsdorff), the First Women's Clinic (Professor Aarno Turunen) and the Second Women's Clinic (Professor Paavo Vara), University of Helsinki, Helsinki, Finland

ACUTE RENAL FAILURE IN PREGNANCY

BY

BÖRJE KUHLBÄCK, OLOF WIDHOLM, BO SKRIFVARS, USKO NIEMINEN, AMOS PASTERNACK, LEIF G. TALLGREN AND JOHAN VON KNORRING

During pregnancy renal changes and pathological conditions of renal origin sometimes develop, among which toxaemia of pregnancy is the most frequent. But other serious disturbances of renal function occur which may suddenly complicate an apparently normal pregnancy. In the early stage the chief cause of renal failure is abortion, often criminal. In these cases an infectious, toxic or haemolytic factor is usually also involved (Anthone *et al.* 1960, Ramsay 1964, Smith *et al.* 1965). Renal failure occurring during the late stage of pregnancy is usually due to abruptio placentae ante tempus, atonic uterine haemorrhage or toxaemia of pregnancy (Bull *et al.* 1955, Merrill, 1965, Atlas and Gaberman, 1958, Knapp and Bonsnes 1960, Alwall 1963, and Smith *et al.* 1965).

This paper deals with the primary cause, the clinical course and the outcome in a series of patients with acute renal complications of pregnancy hospitalized at the Renal Ward during the years 96 196•

Material

The series consists of 2 patients representing about 15 per cent of all cases of acute uraemia treated in the Renal Ward during the years 196 1965. Twelve patients developed renal lesion in connection with abortion during the initial stage of pregnancy

In the majority of these cases infection and/or haemolysis occurred as a complication to the abortion. Fifteen patients developed renal disease in late pregnancy as a complication to abruptio placentae or toxaemia. All patients showed anuria/oliguria and severe renal failure. The majority (21) were haemodialyzed several times on account of severe renal failure manifesting itself as uraemic clinical symptoms and/or pathological laboratory findings elevated creatinine urea and potassium values in the serum and disturbances in the acid-base balance in particular A total of 52 dialyses were performed. Seven patients expired. The renal lesion was diagnosed at autopsy or by percutaneous renal biopsy In three cases the diagnosis was made on the basis of the clinical findings and laboratory results alone.

The patients were admitted to the Renal Ward after observation and treatment in an obstetric hospital for 2–14 days. A stage of hypotonia or shock was discernible in 11 of 16 cases of abortion or ablatio placentae ante tempus In one case a Douglas abscess constituted a source of infection.

No pathogenic bacteria were demonstrable on blood culture. In occasional cases growth of Escherichia coli was observed in the urine, but on admission severe bacterial infection of the urinary tract was not present in a single case. In one case autopsy revealed cortical necrosis of the kidneys

The composition of the series appears in Tables I and II. The course in a typical case is represented diagrammatically (Fig 1)

Discussion

It is generally agreed that the acute renal lesions occurring in female patients are complications of pregnancy in nearly 50 per cent of cases (Ober *et al* 1956) As a rule the prognosis is better in obstetric cases showing renal failure than in cases of acute anuria due to other causes (Bluemle *et al* 1959 Kiley *et al* 1960 Maher and Schreiner 1962 and Alwall, 1963) In the present series too the mortality was relatively low (26 per cent) and it is obvious that the fatal outcome in

Fig Course of the disease in typical case (no 7)

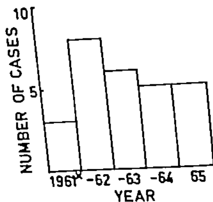


Fig Number of cases during the years 96 -65.

x Renal Ward working only four months

In the majority of these cases infection and/or haemolysis occurred as a complication to the abortion. Fifteen patients developed renal disease in late pregnancy as a complication to abruptio placentae or toxaemia. All patients showed anuria/oliguria and severe renal failure The majority (1) were haemodialyzed several times on account of severe renal failure, manifesting itself as uraemic clinical symptoms and/or pathological laboratory findings elevated creatinine urea and potassium values in the serum and disturbances in the acid-base balance in particular A total of 52 dialyses were performed. Seven patients expired. The renal lesion was diagnosed at autopsy or by percutaneous renal biopsy In three cases the diagnosis was made on the basis of the clinical findings and laboratory results alone

The patients were admitted to the Renal Ward after observation and treatment in an obstetric hospital for 2–14 days. A stage of hypotonia or shock was discernible in 11 of 16 cases of abortion or ablatio placentae ante tempus. In one case a Douglas abscess constituted a source of infection.

No pathogenic bacteria were demonstrable on blood culture. In occasional cases growth of Escherichia coli was observed in the urine but on admission severe bacterial infection of the urinary tract was not present in a single case. In one case autopsy revealed cortical necrosis of the kidneys

The composition of the series appears in Tables I and II The course in a typical case is represented diagrammatically (Fig 1)

Discussion

It is generally agreed that the acute renal lesions occurring in female patients are complications of pregnancy in nearly 50 per cent of cases (Ober *et al* 1956) As a rule the prognosis is better in obstetric cases showing renal failure than in cases of acute anuria due to other causes (Bluemle *et al* 1959 Kiley *et al* 1960 Maher and Schreiner 1962 and Alwall, 1963) In the present series too the mortality was relatively low (26 per cent) and it is obvious that the fatal outcome in seven cases was not chiefly due to the renal lesion but to

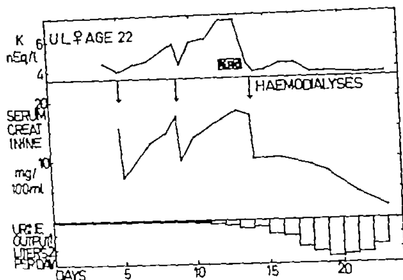


Fig Course of the disease in a typical case (no. 7)

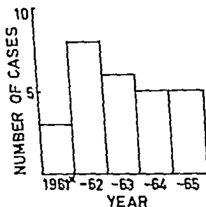


Fig Number of cases during the years 96 -65

Renal Ward working only four months

In the majority of these cases infection and/or haemolysis occurred as a complication to the abortion. Fifteen patients developed renal disease in late pregnancy as a complication to abruptio placentae or toxaemia. All patients showed anuria/oliguria and severe renal failure. The majority (21) were haemodialyzed several times on account of severe renal failure, manifesting itself as uraemic clinical symptoms and/or pathological laboratory findings, elevated creatinine urea and potassium values in the serum and disturbances in the acid-base balance in particular A total of 52 dialyses were performed. Seven patients expired. The renal lesion was diagnosed at autopsy or by percutaneous renal biopsy In three cases the diagnosis was made on the basis of the clinical findings and laboratory results alone

The patients were admitted to the Renal Ward after observation and treatment in an obstetric hospital for 2–14 days. A stage of hypotonia or shock was discernible in 11 of 16 cases of abortion or ablatio placentae ante tempus. In one case a Douglas abscess constituted a source of infection.

No pathogenic bacteria were demonstrable on blood culture In occasional cases growth of Escherichia coli was observed in the urine but on admission severe bacterial infection of the urinary tract was not present in a single case. In one case autopsy revealed cortical necrosis of the kidneys.

The composition of the series appears in Tables I and II. The course in a typical case is represented diagrammatically (Fig 1)

Discussion

It is generally agreed that the acute renal lesions occurring in female patients are complications of pregnancy in nearly 50 per cent of cases (Ober *et al* 1956) As a rule the prognosis is better in obstetric cases showing renal failure than in cases of acute anuria due to other causes (Bluemle *et al* 1959 Kiley *et al* 1960 Maher and Schreiner 1962 and Alwall, 1963) In the present series too the mortality was relatively low (26 per cent) and it is obvious that the fatal outcome in seven cases was not chiefly due to the renal lesion but to

necrosis complicating abortion

Serum Creatinine mg/100 ml		Serum Urea mg/100 ml		Serum Uric Acid mg/100 ml		Creatinine Uric Acid Ratio	Number of Dialyses	Remarks
Before the First Dialysis	After the First Dialysis	Before the First Dialysis	After the First Dialysis	Before the First Dialysis	After the First Dialysis			
10	5.3	280	75	9.4	4.5	1.14	5	Diuresis–recovery
8.25	6.5	3 5	175	7.6	6.7	1.22	6	Diuresis–recovery
11.8	6.65	330	33	17.0	6.6	0.69	3	Diuresis–recovery
11.4	7.4	360	98	4.7	4.9	1.25	4	Diuresis–recovery
17.0	10	–	–	3.8	7.1	1.23	2	Diuresis–recovery
15.3	8.05	530	304	9.5	6.7	3		Diuresis–recovery
15.3	8.0	–	–	–	–	–	3	Diuresis–recovery
8.75	5.4	–	–	24.3	9	0.36		Death 2 days after first dialysis
14.3	7.4	205	80	5.5	7.9	68		Death 3 days after first dialysis
4.5	–	–	–		–	0.44		Diuresis–recovery
4.5	–	93	–		–	0.45	0	Diuresis–recovery
8	6	93	28	5	7	0.52		Extirpatio uteri totalis
								Diuresis–recovery

The anuric stage mostly persisted for several days the maximum being 16 days. The serum creatinine level was high on admission usually over 10 mg/100 ml, the maximum being 5.5 mg/100 ml. The highest creatinine value and the longest period of anuria were noted in patients who recovered. This observation corroborates the view that these patients as a rule do not die of uraemia but of their basic disease or some concurrent complication. The highest serum urea level noted was

Table I. Acute ...

Patient No	Patient Initials	Age Years	Primary Diagnosis	Evacuation & Abrasion, Days before Dialysis or Admission to Renal Ward	Renal Biopsy	Autopsy	[illegible]
1	I. H.	24	Abortus infectus m III Haemolysis	3	+	–	1[illegible]
2	A. K.	31	Abortus infectus m III Haemolysis	2	+	–	9
3	P. V.	25	Abortus asp legalis Haemolysis	7	+	–	6
4	A. K.	[illegible]9	Abortus infect. m II–III Septicaemia. Haemolysis	5	+	–	13
5	A. S.	33	Abortus asp legalis Nephropathia gravid.	5	+	–	11
6	R. H.	28	Abortus provocatus infectus. Peritonitis	4	+	–	4
7	U. L.	22	Abortus m II III	–1	–	–	10
8	M. S.	34	Abortus m III infectus Peritonitis diffusa Abscessus fossae Douglasi	13	–	Peritonitis purulenta. Perforatio fundi uteri	3
9	G. F.	33	Abortus infectus ex usu chinini	3	–	Thrombosis cerebri	5
10	I. L.	25	Abortus infectus m IV	3	–	–	2
11	A. M.	26	Abortus infectus m III	3	+	–	2
12	M-L. K.	36	Abortus retentus m IV Afibrinogenaemia	5	+	–	7

1 day after

necrosis of the liver pancreatitis thrombosis or infection, e.g. peritonitis and sepsis

Renal biopsy and/or autopsy revealed obvious signs of tubular damage (dilated tubuli interstitial oedema casts and debris, often necrotized tubular epithelium) except in the group with toxaemia of pregnancy in which changes of the arteriolae and glomeruli were predominant. In one case renal cortical necrosis was present.

necrosis complicating abortion

Serum Creatinine mg/100 ml		Serum Urea mg/100 ml		Serum Uric Acid mg/100 ml		Creatinine Uric Acid Ratio	Number of Dialyses	Remarks
Before the First Dialysis	After the First Dialysis	Before the First Dialysis	After the First Dialysis	Before the First Dialysis	After the First Dialysis			
10 7	5 3	280	75	9 4	4 5	1 14	5	Diuresis–recovery
8 5	6 5	3 5	75	7 6	6 7	.22	6	Diuresis–recovery
11 8	6 65	330	33	17	6 6	0 69	3	Diuresis–recovery
18 4	7 4	360	198	4 7	4 8	.25	4	Diuresis–recovery
17		—	—	3 8	7	.23		Diuresis–recovery
15 5	6 95	530	304	8 5	6.7	3		Diuresis–recovery
15 3	8	—	—	—	—	—	3	Diuresis–recovery
6 75	5 4		—	24 3	13 9	0 38		Death 2 days after first dialysis
10 5	7 4	205	80	15 5	7 8	0 68		Death 3 days after first dialysis
4 5		—	—		—	0 44		Diuresis–recovery
4 5		93	—		—	0 45		Diuresis–recovery
8	6	93	28	5	7 0	52		Exstirpatio uteri totalis Diuresis–recovery

The anuric stage mostly persisted for several days, the maximum being 16 days. The serum creatinine level was high on admission usually over 10 mg/100 ml, the maximum being 25 5 mg/100 ml. The highest creatinine value and the longest period of anuria were noted in patients who recovered. This observation corroborates the view that these patients as a rule do not die of uraemia but of their basic disease or some concurrent complication. The highest serum urea level noted was

Table II. Continued

Patient N	Patient Initials	Age Years	Primary diagnosis	Renal Biopsy	Autopsy	Anuria (< 100 ml/day) Days	Serum Creatinine mg/100 ml: Before the First Dialysis	Serum Creatinine mg/100 ml: After the First Dialysis
13	U. R.	19	Ablatio placentae ante tempus. Nephropathia gravid.	+	–	4	16.30	7.55
14	A. L.	24	Ablatio placentae ante tempus	+	–	16	15.00	7.60
15	H. K.	[illegible]	Ablatio placentae ante tempus	+	–	3	11.90	–
16	L. K.	45	Ablatio placentae ante tempus	+	–	5	14.50	8.40
17	H. V.	35	Toxaemia gravidarum	–	–	7	13.20	6.50
18	E. T.	20	Toxaemia gravidarum	–	Atrophia acuta hepatis. Necrosis corticalis renum	5	5.70	–
19	A. T.	33	Toxaemia gravidarum	+	–	oliguria	15.00	[illegible]
20	S. K.	31	Toxaemia gravidarum *Afibrinogenaemia*	–	Necroses hepatis	7	12.90	6.85
21	H. P.	29	Toxaemia et eclampsia Graviditas m V–VI	–	Necroses hepatis. Pancreatitis	4	10.70	6.50
22	T. N.	33	Nephropathia gravidarum	+	Pancreatitis Pericarditis uraemica	5	17.40	8.85
23	S. R.	38	Nephropathia gravidarum	–	Necroses hepatis. Necrosis et haemorrh. hypophyseos et gl. suprarenales	6	15.90	7.65
24	S. G.	31	Nephropathia gravidarum. Lupus erythematosus	+	–	6	17.10	10.70
25	I. H.	23	Crisis hypertonicus post partum	+	–	7	13.20	7.85
26	K. K.	40	Graviditas extrauterina. Haemorrhagia intra-abdominalis	+	–	oliguria	6.65	–
27	B. S.	22	Graviditas m VIII. Haemolysis. Transfusio foetomaternalis	+	–	1	3.75	–

Delivery one day before admission to renal ward.
Delivery 18 days before admission to renal ward.
Delivery four days before admission to renal ward.

ailure in late pregnancy

Serum Urea mg/100 ml		Serum Uric Acid mg/100 ml		Creatinine Uric Acid Ratio	Condition of the Foetus	Number of Dialyses	Remarks
Before the First Dialysis	After the First Dialysis	Before the First Dialysis	After the First Dialysis				
–	–	10	7.5	0.86	Sectio Caesarea Foetus mortuus	2	Diuresis-recovery
–	–	8.9	9.4	79	Sectio Caesarea Foetus mortuus	3	Diuresis-recovery
–	–	3	–	0.97	Sectio Caesarea Foetus mortuus		Diuresis-recovery
–	–	24.4	3.6	0.59	Sectio minor		Diuresis-recovery
–	–	34.8	7.6	38	Sectio Caesarea Normal	2	Diuresis-recovery
123	–	30.5	–	9	Foetus mortuus		Death 4 days after delivery
–	–	–	–	–	Sectio Caesarea		Diuresis-recovery
[illegible]	165	5	0.4	51	Sectio Caesarea	2	Death 3 days after delivery
[illegible]	75	16.5	3	65	Sectio Caesarea Foetus mortuus	3	Death 7 days after first dialysis
[illegible]	206	3.6	6.9	28	Foetus mortuus[a]	5	Death 43 days after first dialysis
–	–	–	–	–	Sectio Caesarea		Death days after first dialysis
[illegible]	292	20	[illegible]	85	Sectio Caesarea		Diuresis-recovery
[illegible]	50	4.5	8.6	9	Normal[b]	2	Diuresis-recovery
–	–	8.9	–	87	Foetus mortuus[a]		Diuresis-recovery
75		3	–		Foetus mortuus[a]		Diuresis-recovery

Operation 14 days before admission to renal ward.
Delivery on the second day in renal ward.

Table II. Acute renal

Patient No	Patient Initials	Age Years	Primary diagnosis	Renal Biopsy	Autopsy	Anuria (< 200 ml/day) Days	Serum Creatinine mg/100 ml Before the First Dialysis	Serum Creatinine mg/100 ml After the First Dialysis
13	U. R.	19	Ablatio placentae ante tempus. Nephropathia gravid.	+	–	4	16.30	7.05
14	A. L.	24	Ablatio placentae ante tempus	+	–	16	15.00	7.60
15	H. K.	27	Ablatio placentae ante tempus	+	–	3	11.90	–
16	L. K.	45	Ablatio placentae ante tempus	+	–	5	14.50	8.40
17	H. V.	35	Toxaemia gravidarum	–	–	7	13.20	6.50
18	E. T.	20	Toxaemia gravidarum	–	Atrophia acuta hepatis. Necrosis corticalis renum	5	5.70	–
19	A. T.	33	Toxaemia gravidarum	+	–	oliguria	15.00	.00
20	S. K.	31	Toxaemia gravidarum. Afibrinogenaemia	–	Necroses hepatis	7	12.90	6.85
21	H. P.	29	Toxaemia et eclampsia. Graviditas m. V–VI	–	Necroses hepatis. Pancreatitis	4	10.70	6.50
22	T. N.	33	Nephropathia gravidarum	+	Pancreatitis. Pericarditis uraemica	5	17.40	9.85
23	S. R.	38	Nephropathia gravidarum	–	Necroses hepatis. Necrosis et haemorrh. hypophyseos et gl. suprarenales	6	15.90	05
24	S. G.	31	Nephropathia gravidarum. Lupus erythematosus	+	–	6	17.10	10.70
5	L. H.	23	Crisis hypertonicus post partum	+	–	7	13.20	95
26	K. K.	40	Graviditas extrauterina. Haemorrhagia intra-abdominalis	+	–	oliguria	6.65	–
7	B. S.	22	Graviditas m. VIII. Haemolysis. Transfusio foetomaternalis	+	–	1	3.75	–

Delivery one day before admission to renal ward.
Delivery 18 days before admission to renal ward.
Delivery four days before admission to renal ward.

ailure in late pregnancy

Serum Urea mg/100 ml		Serum Uric Acid mg/100 ml		Creatinine Uric Acid Ratio	Condition of the Foetus	Number of Dialyses	Remarks
Before the First Dialysis	After the First Dialysis	Before the First Dialysis	After the First Dialysis				
—	—	19	7.5	86	Sectio Caesarea Foetus mortuus	2	Diuresis–recovery
—	—	18.9	9.4	0.79	Sectio Caesarea Foetus mortuus	3	Diuresis–recovery
—	—	3	—	0.97	Sectio Caesarea Foetus mortuus		Diuresis–recovery
—	—	24.4	3.6	0.59	Sectio minor	2	Diuresis–recovery
—	—	34.8	7.6	38	Sectio Caesarea Normal		Diuresis–recovery
173	—	30.5	—	9	Foetus mortuus[1]		Death 4 days after delivery
—	—	—	—	—	Sectio Caesarea		Diuresis–recovery
18	263	25	4	51	Sectio Caesarea	2	Death 3 days after delivery
176	73	18.5	0.3	65	Sectio Caesarea Foetus mortuus	3	Death 7 days after first dialysis
226	206	3.6	6.9	28	Foetus mortuus[2]	5	Death 43 days after first dialysis
—	—	—	—	—	Sectio Caesarea		Death days after first dialysis
283	192	20	9	85	Sectio Caesarea	1	Diuresis–recovery
280	90	4.5	8.6	9	Normal[4]	2	Diuresis–recovery
—		9.8		0.67	Foetus mortuus		Diuresis–recovery
75		3	—		Foetus mortuus		Diuresis–recovery

Operation 4 days before admission to renal ward.
Delivery on the second day in renal ward.

530 mg/100 ml The largest number of haemodialyse performed in one and the same case was six. Strikingly high uric acid values in the serum were noted in particular in the group with toxaemia of pregnancy This observation has been reported earlier (Kuhlback and Widholm 1964) In the group in question the ratio creatinine/uric acid was under 1 in all cases but one (Table II)

In the present cases the development of acute renal failure must be regarded as resulting from either the hypotensive phase which was demonstrable in connection with the complication of pregnancy (haemorrhagia, sepsis hypovolaemia, toxic effect) or from intravascular haemolysis or changes of the arterioles and glomeruli in toxaemia of pregnancy Even where it cannot be proved that the measurable blood pressure is decreased, the renal blood flow may already be markedly reduced with tubular damage resulting (Ramsay 1964)

The toxic hypotensive phase occurring in septic abortion has recently been discussed in detail by Douglas and Beckmann (1966) on the basis of 50 cases and by Gatzmuri and Katz (1966) who reviewed 143 cases In addition to haemorrhagia the central mechanism in this severe syndrome is the entrance of pathogenic endo- and exotoxin forming bacteria in the pregnant uterus. The most frequent bacteria are *Escherichia coli Pseudomonas aeruginosa* and *Clostridium Welchii*. The last-mentioned bacterium in particular has been encountered in cases where criminal abortion may be suspected, and it is likely to cause the septic toxic picture often associated with haemolysis which is seen in these cases. It goes without saying that effective antibacterial therapy has to be instituted In addition, the shock requires adequate intensive treatment. Furthermore, in many cases early evacuation of the uterus, or even hysterectomy is indicated in order to eliminate the causes of persistent sepsis endotoxin shock and hypotonia. In the present series pathogenic bacteria were not demonstrated by blood culture in a single case This may be due to the fact that the patients have been intensively treated with antibiotics in an obstetric hospital before referral to the Renal Ward.

In certain cases it must be assumed that fibrinogen deposits

develop chiefly in the hepatic, pulmonary cerebral and renal vessels (Moore, 1966) As a result, low fibrinogen values are obtained in the blood, and a risk of haemorrhage obviously persists. Direct fibrinolysis may also be present. Hypofibrinogenaemia (fibrinogen 0,4 and 0 7 g/l, respectively) occurred in two of the present cases (nos. 12 and 20) In such cases fibrinogen and, perhaps, heparin treatment should be meditated. At the same time the administration of low molecular dextran (Rheomacrodex) and mannitol is indicated.

Occasionally sudden haemolysis resulting in renal failure may occur during pregnancy without any apparent cause. In case 27 which recently has been described in another connection (Pasternack et al 1966) this was attributed to transplacental foeto-maternal transfusion of incompatible blood. In this connection it may be mentioned that Zilliacus (1961) and Vartiainen (1963) have demonstrated the presence of foetal cells in the maternal blood in 9–9.5 per cent of cases.

Patients with severe, acute eclamptic nephropathy in the late stage of pregnancy often succumb to a combination of cerebral oedema, pulmonary oedema and uraemia. The presence of severe liver damage often contributes to the fatal outcome in these cases (Ikonen, 1964) In the present series liver damage was observed in cases 18 20, 21 and 23. In all of them the liver lesion was the chief cause of death.

Furthermore acute renal failure occurs in pregnant patients with latent chronic glomerulo- or pyelonephritis (Sims 1965) In this group the pathogenesis is more obvious, however and no such cases are included in the present series.

In order to prevent the development of renal lesions in connection with the hypotonic states discussed above, the most important measures undoubtedly are the institution of antibacterial therapy as soon and as effectively as possible and the restoration of normal haemodynamics. For this purpose blood transfusions and infusions of low molecular dextran and mannitol are indispensable. During the time that mannitol has been in use ther has been a decrease in the number of obstetric cases remitted to the Renal Ward for dialysis (Fig 2) This seems to be attributable to a marked improvement of the initial treat

530 mg/100 ml The largest number of haemodialyse performed in one and the same case was six. Strikingly high uric acid values in the serum were noted in particular in the group with toxaemia of pregnancy This observation has been reported earlier (Kuhlbäck and Widholm, 1964) In the group in question the ratio creatinine/uric acid was under 1 in all cases but one (Table II)

In the present cases the development of acute renal failure must be regarded as resulting from either the hypotensive phase which was demonstrable in connection with the complication of pregnancy (haemorrhagia sepsis hypovolaemia, toxic effect) or from intravascular haemolysis or changes of the arterioles and glomeruli in toxaemia of pregnancy Even where it cannot be proved that the measurable blood pressure is decreased, the renal blood flow may already be markedly reduced with tubular damage resulting (Ramsay 1964)

The toxic hypotensive phase occurring in septic abortion has recently been discussed in detail by Douglas and Beckmann (1966) on the basis of 50 cases and by Gatzmuri and Katz (1966) who reviewed 143 cases. In addition to haemorrhagia the central mechanism in this severe syndrome is the entrance of pathogenic, endo- and exotoxin forming bacteria in the pregnant uterus. The most frequent bacteria are *Escherichia coli Pseudomonas aeruginosa* and *Clostridium Welchii* The last-mentioned bacterium in particular has been encountered in cases where criminal abortion may be suspected, and it is likely to cause the septic toxic picture often associated with haemolysis which is seen in these cases. It goes without saying that effective antibacterial therapy has to be instituted in addition the shock requires adequate intensive treatment. Furthermore in many cases early evacuation of the uterus, or even hysterectomy is indicated in order to eliminate the causes of persistent sepsis endotoxin shock and hypotonia. In the present series pathogenic bacteria were not demonstrated by blood culture in a single case This may be due to the fact that the patients have been intensively treated with antibiotics in an obstetric hospital before referral to the Renal Ward.

In certain cases it must be assumed that fibrinogen deposits

of mannitol in an early stage is emphasized. In the presence of renal damage, active nephrological treatment should be instituted haemo- or peritoneal dialyses are often indispensable.

REFERENCES

Alwall N Therapeutic and diagnostic problems in severe renal failure. Scand University Books Stockholm, 1963

Anthone S Anthone R, and *Doyle J E*, Obst. & Gynec. 5, 146, 1960

Atler D and *Gabermen P* Reversible Renal Insufficiency The Williams & Wilkins CO Baltimore, 1958

Bluemle L W Webster G D and *Elkinton J R* Arch. Int. Med. 04, 80, 1959

Bull, G. M Joekes A. M. and *Lowe K. G* Lancet 57 1955

Doughlas G W and Beckman E. M. Am. J Obst & Gynec. 96 633, 966

Garewari, R. and *Katz E.*, Abstr Internat. Congr Nephrol. 47 966

Ikonen E Jaundice in late pregnancy Acta obst. et gynec. scandinav Suppl. 5, 964

Kiley J E Powers S R. and *Beebe R T* New Engl. J. Med. 262, 48 1960

Knapp R C and *Bonnars R W* Clin. Obst. & Gynec 3, 7 8, 960

Kuhlbäck B and Widholm O., Acta obst. et gynec scandinav 43, 330 964

Maher J F and *Schreiner G. E.*, Arch. Int. Med. 492, 96

Merrill, J P The Treatment of Renal Failure Grune & Stratton, New York, 965

Moore J G Am. J Obst. & Gynec 96 64 966

Ober W B Reid D E Romney S L and Merrill J P Am. J Med. 21 78 956

Pasternack A Forsskåhl U von Knorring, J Skrifvars B and Kuhlbäck B Acta med. scandinav 80 3, 966

Romney A G Clin Obst & Gynec 7 18, 964

Sims E Ann Rev Med 16 221 965

Smith K *Browne J C* Shackman, R. and *Wrong, O M* Lancet 35 965

Vartiainen E Acta med scandinav Suppl. 308 174, 965

Zillucus H Med Welt 35, 75 96

Received on March 7th, 967

ment in particular perhaps to the increased use of mannitol. It seems also probable that the obstetricians more than before have taken the risk of renal failure into account and in time have instituted adequate treatment.

In the presence of renal damage effective nephrological treatment should be given in a renal ward and in an early stage rather than too late. In addition to usual methods of treating anuria uraemia, including the management of hyperkalaemia, hypocalcaemia and acidosis early (prophylactic) and frequent haemo- or peritoneal dialyses should be resorted to. By the aid of intensive dialytic treatment it is possible to save many patients who would otherwise succumb to uraemia and electrolyte disturbances. Unfortunately there still remains one group of patients who die of severe sepsis endotoxinaemia, renal cortical necrosis or toxaemia of pregnancy with liver damage and pulmonary and cerebral oedema.

SUMMARY

Twenty-seven patients with acute renal failure during pregnancy were treated at the Renal Ward during the years 1961–1965. These patients constituted about 15 per cent of all acute cases of uraemia treated by dialysis during this period. In 12 cases renal lesion developed in connection with abortion in the initial stage of pregnancy. In the majority of these cases infection and/or haemolysis was also present. In 15 cases the renal damage developed in late pregnancy as a complication to abruptio placentae or toxaemia. All patients showed anuria-oliguria and severe renal failure. Twenty-one patients were haemodialyzed the total number of haemodialyses performed was 5. Seven patients died. In one case autopsy revealed renal cortical necrosis.

The causes of renal lesion as well as the clinical features, the course of the disease and the outcome are discussed. It is emphasized that the fatal outcome in seven cases was not chiefly due to the renal lesion but to necrosis of the liver pancreatitis or thrombosis, or to infection, e.g. peritonitis or sepsis. The principles of management are discussed, and the administration

of mannitol in an early stage is emphasized. In the presence of renal damage active nephrological treatment should be instituted haemo- or peritoneal dialyses are often indispensable.

REFERENCES

Aberg N Therapeutic and diagnostic problems in severe renal failure. Scand. University Books, Stockholm, 963
Anthone S Anthone R, and Doyle J E, Obst. & Gynec. 15 46 960
Arias D and Gaberman P Reversible Renal Insufficiency The Williams & Wilkins CO Baltimore 1958
Bluemle L W Webster G D and Elkinton, J R Arch. Int. Med. 104, 180, 1959
Bull, G M Joekes A M and Lowe K G Lancet 152, 955
Douglas G. W and Beckman E M Am J Obst. & Gynec. 96 633, 966
Garnsart, R. and Katz E, Abstr Internat. Congr Nephrol. 47 966
Ilonen E Jaundice in late pregnancy Acta obst. et gynec. scandinav Suppl. 5, 964
Kiley J E Powers, S R. and Beebe R T New Engl J Med. 262, 481 960
Knapp R C., and Bowmen R W Clin. Obst. & Gynec. 3, 7 8, 960
Kuhlbäck B and Widholm O Acta obst. et gynec scandinav 43, 330 1964
Maher J F and Schreiner G E Arch. Int. Med. 0 493, 962
Merrill J P The Treatment of Renal Failure. Grune & Stratton, New York, 965
Moore J G Am J Obst & Gynec. 96 64 968
Ober W B. Reid D E Romney S. L and Merrill, J P Am. J. Med. 78 956
Pasternack A Forsbjelm U von Knorring, J Skrifvars B and Kuhlbäck B Acta med scandinav 180 2, 966
Ramsay A G Clin Obst & Gynec. 7 8, 964
Sims E Ann Rev Med 16 221 965
Smith K Browne J C Shackman, R. and Wrong, O M. Lancet 2 35 965
Vartiainen E Acta med scandinav Suppl 398, 174, 963
Zilliacus H Med Welt 35 75 96

Received on March 7th, 967

ment in particular perhaps to the increased use of mannitol. It seems also probable that the obstetricians more than before have taken the risk of renal failure into account and in time have instituted adequate treatment.

In the presence of renal damage effective nephrological treatment should be given in a renal ward, and in an early stage rather than too late. In addition to usual methods of treating anuria uraemia, including the management of hyperkalaemia, hypocalcaemia and acidosis early (prophylactic) and frequent haemo- or peritoneal dialyses should be resorted to. By the aid of intensive dialytic treatment it is possible to save many patients who would otherwise succumb to uraemia and electrolyte disturbances. Unfortunately there still remains one group of patients who die of severe sepsis, endotoxinaemia, renal cortical necrosis or toxaemia of pregnancy with liver damage and pulmonary and cerebral oedema.

SUMMARY

Twenty-seven patients with acute renal failure during pregnancy were treated at the Renal Ward during the years 1961–1965. These patients constituted about 15 per cent of all acute cases of uraemia treated by dialysis during this period. In 12 cases renal lesion developed in connection with abortion in the initial stage of pregnancy. In the majority of these cases infection and/or haemolysis was also present. In 15 cases the renal damage developed in late pregnancy as a complication to abruptio placentae or toxaemia. All patients showed anuria-oliguria and severe renal failure. Twenty-one patients were haemodialyzed, the total number of haemodialyses performed was 52. Seven patients died. In one case autopsy revealed renal cortical necrosis.

The causes of renal lesion as well as the clinical features, the course of the disease and the outcome are discussed. It is emphasized that the fatal outcome in seven cases was not chiefly due to the renal lesion but to necrosis of the liver, pancreatitis or thrombosis or to infection, e.g. peritonitis or sepsis. The principles of management are discussed, and the administration

of mannitol in an early stage is emphasized. In the presence of renal damage, active nephrological treatment should be instituted haemo- or peritoneal dialyses are often indispensable.

REFERENCES

Alwall N Therapeutic and diagnostic problems in severe renal failure. Scand University Books, Stockholm, 963

Anthony S Anthony R., and *Doyle J E.* Obst. & Gynec. 5 46 1960

Arlas D and *Gaberman, P* Reversible Renal Insufficiency The Williams & Wilkins CO Baltimore, 1958

Bluemle L W Webster G D and *Elkinton J R.*, Arch. Int. Med. 104 60 1959

Bull G M Joekes A. M., and *Lowe K. G* Lancet 52 1955

Donghlas G W and *Beckman E. M.*, Am. J. Obst. & Gynec. 96 633, 966

Gattomari R., and *Katz E.*, Abstr Internat. Congr Nephrol. 47 966

Ikonen E Jaundice in late pregnancy Acta obst. et gynec. scandinav Suppl. 5, 964

Kilby J E Powers S R. and *Berbe R. T* New Engl. J Med. 26 48 1960

Knapp R. C and *Bowers R. W* Clin Obst. & Gynec. 3, 7 8, 1960

Kuhlbäck B and *Widholm O* Acta obst. et gynec. scandinav 43, 330 1964

Maher J F and *Schreiner G E.*, Arch Int. Med 1 0 403, 962

Merrill J P The Treatment of Renal Failure. Grune & Stratton, New York, 965

Moore J G Am J Obst & Gynec. 96 641 966

Ober W B Reid, D E Romney S L and *Merrill J P* Am. J Med. 21 78 956

Pasternack A Fernchjelm, U von Knorring, J Skrifvars B., and *Kuhlbäck, B* Acta med scandinav 80 3, 966

Romney A G Clin Obst & Gynec. 7 2 9 964

Sons E Ann Rev Med 16 221 1965

Smith K Browne J C Shackman R., and *Wrong, O M* Lancet 2 351 965

Vartiainen E Acta med scandinav Suppl. 398, 174 1963

Zilliacus H Med Welt 35, 731 98

Received on March 7th, 967

Luukkainen Tapani, Väistö Leila, and Järvinen Pentti A Acta obstet et gynec scandinav 46, 486, 1967

From the Second Department of Obstetrics and Gynaecology (Prof P Vara), Central University Hospital Helsinki Finland

THE EFFECT OF ORAL INTAKE OF ETHYL ALCOHOL ON THE ACTIVITY OF THE PREGNANT HUMAN UTERUS

BY

TAPANI LUUKKAINEN LEILA VÄISTÖ AND PENTTI A. JÄRVINEN

It has been demonstrated by Fuchs and Wagner (1963) that the release of oxytocin in puerperal rabbits is inhibited by intravenous alcohol infusion and that oral administration of alcohol inhibits the contractions produced by suckling in the human uterus 3–4 days after delivery It seems that oxytocin release in rabbit parturition can be inhibited by the administration of alcohol (Fuchs 1964) The results of a clinical trial based on these observations using the intravenous route for the administration of ethanol have been published by Fuchs (1965)

This paper reports the results of a study on the effect of oral intake of ethanol on uterine activity during the first stage of term labour and on patients admitted to the hospital because of threatened premature labour

PART 1

Material and Methods

Sixteen normal parturients who were in the first stage of labour and had intact membranes were selected for this part of the study The age of these patients varied between 20 and 37 years. There were 8 primiparae in this series. The duration of the

pregnancy at labour was between 40–42 weeks, except for one patient, who was 39 weeks pregnant. All patients in this series had a single pregnancy and gave birth to a living, mature, and healthy child.

The uterine pressure was first recorded with an external guard ring tocograph for one hour to determine the basal activity of the uterine musculature. After registration of the basal activity the patients were twice given 30 ml of cognac, containing 34 per cent ethanol by weight per volume. The interval between the intakes of ethanol was 15 minutes. The second intake of alcohol was taken as the start of a two-hour experimental recording period. This experimental period was divided into three periods of 40 minutes each, which were compared separately with the last 40-minute period of the basal activity recording, as regards both the number of contractions and the total area of the contractions. The statistical analysis was made by the t-test.

Results

The results were evaluated by analyzing the recording of uterine activity. The basal activity was compared with the three experimental recording periods each of forty minutes, after the intake of alcohol. Period I is thus 0–40 minutes after the alcohol intake, period II and period III are from 41 to 80 and from 81 to 120 minutes respectively. The uterine activity was determined by counting the number of contractions during each forty-minute period and measuring with a planimeter the total area of the contractions during each period. The calculated uterine activities obtained with both methods during each period were compared with respective activity measured during the basal recording period before the alcohol intake.

The results of the statistical treatment of the data are presented in Table I. It can be observed that the number of contractions was already significantly decreased during the first 40 minutes. The depression of uterine activity continued during the other two forty-minute periods but the inhibition was strongest during the first 40 minutes. The results are about the

Table I. *The Effect of 20 g Pure Alcohol on the Number and Area of Uterine Contractions of Patients in the First Stage of Labour*

		Number of Patients	Mean of Differences	t	P
Number of Contractions	Before/Period I	16	− 2.69	4.22	0.001
	Before/Period II	16	− 1.94	2.85	0.05
	Before/Period III	16	− 1.56	2.42	0.05
	Period I/Period II	16	+ 0.812	2.93	0.05
Area	Before/Period I	16	−18.4	7.08	0.001
	Before/Period II	16	− 8.9	2.36	0.05
	Before/Period III	16	− 6.0	1.16	–
	Period I/Period II	16	+ 7.1	3.14	0.01

Recording periods 40 minutes. Before = period before alcohol intake. Period I–III are recorded after alcohol intake

Table II. *Age and Parity of Patients Treated with Oral Alcohol for Threatened Premature Labour*

Age in Years	Parity							
	I	II	III	IV	V	VI	VII	
Under 20	2	1						3
21–30	7	6	5				1	19
31–35	3	2	3		3	1	1	13
36–40	1			2	1	1		5
Total	13	9	8	2	4	2	2	40

same when the activity of the uterus is measured by the area of the contractions but no depression of activity can be demonstrated during the last recording period however the number of contractions was still less than the basal value which means that the intensity of the contractions increased during the period of 81–120 minutes after alcohol intake

Table III. *Duration of Pregnancy on Admission and Maturity of the Children at Birth in Patients with Intact Membranes Treated with Oral Alcohol*

Weeks of pregnancy on admission	Status of child at birth			
	Premature	Mature	Stillbirth	
Under 24			1	2
5 28	1	1		2
29–30		1		2
3 32	3	3		7
33–34	3			5
35–36	2			3
37–		4		4
Total	8	13	3	25

Table IV *Duration of Pregnancy at Admission and Maturity of the Children at Birth in Patients with Ruptured Membranes Treated with Oral Alcohol*

Weeks of pregnancy at admission	Status of child at birth			
	Premature	Mature	Stillbirth	
Under 24				1
5 28	1			
29–30		1		3
3 32	3			3
33–34				4
35–36				
37–				
Total	8	6		15

PART 2

Material and Methods

The second material consists of 40 patients admitted because of threatened premature labour The membranes had ruptured at admission in 15 of the 40 patients. The distribution of the series according to age and parity is given in Table II. Most of the patients were less than quadriparous and under 35 years old These forty patients had had 109 deliveries before the cur

rent pregnancy and in 11 of them 27 abortions had occurred. The disorders complicating this pregnancy were urinary infection in seven patients and anaemia (haemoglobin below 12.0 g/100 ml) in 23 patients three of whom had haemoglobin below 10.0 g/100 ml. The duration of the pregnancy at admission was between 18–39 weeks (Tables III and IV).

Treatment was started immediately by giving 30 ml of cognac three times per day. Bed rest was instituted but no other treatment such as gestagens was given. Only the patients with urinary infection and those with ruptured membranes received antibiotics or sulfa preparations. The anaemic patients were treated as usual by iron therapy. The duration of the treatment with alcohol was between 2–49 days.

Results

The patients with intact membranes and those with ruptured membranes at admission were analyzed separately.

Patients with intact membranes. The data on duration of the pregnancy and the effect of the oral alcohol treatment are presented in Table III. The criterion for prematurity was the birth weight: infants below 2500 g were regarded as premature. It can be observed that 13 of the 25 patients gave birth to a mature child and 9 of them to a premature. Intrauterine foetal death was suspected in three of the patients in this series, because examination revealed no heart sounds and the patient had not felt any foetal movements on the day of admission. They were likewise treated with the oral alcohol until the diagnosis of intrauterine foetal death was definite; then the treatment was discontinued and delivery was induced the following day with a high dose of intravenous oxytocin. These three patients delivered macerated foetuses weighing between 620–1600 g.

The nine patients who gave birth to premature infants all had one or two disorders complicating pregnancy. Anaemia was found in five of them, three had a urinary infection and seven out of nine had toxaemia. Two of these disorders were concurrent in six patients. Because of intrauterine foetal distress an elective Caesarean section had to be performed on two out of these nine

patients. The pregnancy of four patients had to be terminated by induction of labour because of severe pre-eclampsia, the foetus being viable. Only three out of these nine delivered spontaneously before the maturity of the child, in spite of the treatment.

Patients with ruptured membranes. Table IV shows the duration of the pregnancy and the effect of the oral alcohol treatment in the group of 15 women who had threatened labour and ruptured membranes when admitted. There was one patient with suspected intrauterine death at the time of admission labour was induced and the diagnosis found to be correct. She delivered macerated twins weighing 300 g and 400 g. During the treatment, but more than 48 hours after the start of the alcohol intake, eight patients delivered viable but premature infants. Three out of these eight patients had twins, whose birthweights were between 1230 g and 2230 g. Anaemia was diagnosed in seven out of these eight patients. In these eight women delivery was postponed by 2 to 30 days as a result of the treatment. In the remaining six women delivery was postponed until the delivery of a mature child.

If the results in the two groups are combined, it can be observed that out of 40 patients who were more than 18 weeks pregnant and had to be hospitalized because of threatened premature labour 19 gave birth to a mature healthy child and 17 had a premature delivery which, however was postponed until the foetus was viable. Except for four intrauterine deaths prior to admission, all patients gave birth to a living child. There was neither discomfort nor complication due to the oral treatment with alcohol

Discussion

In the first part of the present investigation it was shown that a dose equivalent to 20 g pure alcohol given orally was able to inhibit uterine activity in the first stage of labour The effect is surprisingly rapid but of relatively short duration, being from 40 to 80 minutes. The results of the second part of this study seem to demonstrate that the effect is more pronounced before term, because after receiving only 10 g of pure alcohol orally

rent pregnancy and in 11 of them 27 abortions had occurred. The disorders complicating this pregnancy were urinary infection in seven patients and anaemia (haemoglobin below 11.0 g/100 ml) in 23 patients three of whom had haemoglobin below 10.0 g/100 ml. The duration of the pregnancy at admission was between 18–39 weeks (Tables III and IV)

Treatment was started immediately by giving 30 ml of cognac three times per day Bed rest was instituted but no other treatment such as gestagens was given. Only the patients with urinary infection and those with ruptured membranes received antibiotics or sulfa preparations. The anaemic patients were treated as usual by iron therapy The duration of the treatment with alcohol was between 2–49 days

Results

The patients with intact membranes and those with ruptured membranes at admission were analyzed separately

Patients with intact membranes The data on duration of the pregnancy and the effect of the oral alcohol treatment are presented in Table III The criterion for prematurity was the birth weight infants below 2500 g were regarded as premature. It can be observed that 13 of the 25 patients gave birth to a mature child and 9 of them to a premature Intrauterine foetal death was suspected in three of the patients in this series, because examination revealed no heart sounds and the patient had not felt any foetal movements on the day of admission. They were likewise treated with the oral alcohol until the diagnosis of intrauterine foetal death was definite then the treatment was discontinued and delivery was induced the following day with a high dose of intravenous oxytocin. These three patients delivered macerated foetuses weighing between 620–1600 g.

The nine patients who gave birth to premature infants all had one or two disorders complicating pregnancy Anaemia was found in five of them three had a urinary infection and seven out of nine had toxaemia Two of these disorders were concurrent in six patients. Because of intrauterine foetal distress an elective Caesarean section had to be performed on two out of these nine

Acknowledgements

The authors wish to thank Dr Anna Riitta Fuchs and Fritz Fuchs for placing at disposal the results of their preliminary experiments.

REFERENCES

Bueno-Montano M, Mcgaughey H S., Herbert G M., and Thornton W N Am J. Obst. & Gynec. 94 1 966

Fuchs A.-R., J Endocrinol. 30 17 1964

2nd Internat. Congr Endocrinol London, Excerpta Medica Congr Series No 83, 753, 965

Fuchs A.-R., and Wagner G Acta Endocrinol. 44 593, 1963

Nature 98 92 963

Fuchs F J Obst. & Gynaec. Brit Commonw 72 965

Hirvonen P A., and Laukkabeturo T Ann. chir gynaec. Fenniae 51 438, 962

Smyth C N J Obst gynaec Brit Emp. 64 45, 957

Received on Nov 16, 966

three times per day a high percentage of patients gave birth to a mature infant A previous investigation from this hospital showed that in spite of all other medication 50 per cent of patients having a premature rupture of membranes delivered in 18 1/2 hours from the rupture of the membranes The oral alcohol treatment postponed delivery in similar patients by more than 48 hours in every case and when the membranes were intact delivery was postponed by more than 120 hours.

The beneficial effect of oral alcohol in the treatment of threatened abortion cannot be evaluated in the light of the results of the present investigation, because the material was selected to be over 18 weeks pregnant to avoid a high percentage of abnormalities in the conceptus accompanying the threatened abortion.

The experimental work of Anna Riitta Fuchs has demonstrated that the release of oxytocin can be inhibited by an alcohol infusion. The question whether the small amounts of alcohol given orally in this study inhibit oxytocin release and thereby prevent premature labour remains to be answered when methods of determining low concentrations of oxytocin in blood during pregnancy are available

It seems at the present very likely that in addition to the inhibition of oxytocin release the beneficial effect of oral alcohol as a uterine relaxant may be due to a direct effect on the myometrium

SUMMARY

The effect of oral alcohol on uterine activity was studied in sixteen normal parturients in the first stage of labour A significant inhibition of uterine activity was observed during 80 minutes after alcohol intake

Forty patients hospitalized because of a threatened premature labour were treated with alcohol given orally Nineteen of them gave birth to a mature child and seventeen had a premature labour but the child was viable The remaining four already had a missed abortion at the start of the treatment.

and chorionic gonadotrophin (HCG) promote transhydrogenation. A preliminary report has been published as a congress abstract (1966)

Materials and Methods

The numbers of different types of placentae examined in the study are given in Table I

Isolation of enzyme from placental tissue

Immediately after its expulsion, the placenta was placed in ice and dissected. A sufficient amount of placental tissue freed from membrane and connective tissue was washed in 0.15 M potassium chloride solution until the wash solution remained clear The tissue was added in the ratio of one gram to 4 millilitres to a solution of pH 7.0 (I) that was 0.01 M in monopotassium phosphate and 0.005 M in dipotassium ethylenediaminetetra-acetate and contained 20 per cent (v/v) glycerol and the mixture was homogenized in a Potter-Elvehjem homogenizer The homogenate was then centrifuged at 57 000×g for 60 minutes. Ammonium sulphate was added to the supernatant until its concentration was 40 per cent of the saturation concentration and the supernatant was left to stand two hours before it was centrifuged at 10 000×g for 30 minutes. The final supernatant contained no enzyme. The precipitate was dissolved in a small volume of a solution (II) of pH 7.0 which was 0.01 M in monopotassium phosphate and 0.005 M in dipotassium ethylenediaminetetra-acetate and contained 50 per cent (v/v) glycerol The enzyme activity of the solution was determined immediately as follows A mixture 3.0 ml in volume was prepared from 300 micromoles of Tris buffer solution, 1 5 micromoles of NAD 6 0 micromoles of sodium dl-isocitrate 0.075 micromole of NADP 0 22 micromole of 17β-oestradiol dissolved in 50 microliters of 96 per cent ethanol, 1 m-I U of isocitrate dehydrogenase (Sigma) 70 micromoles of manganese sulphate tetrahydrat and an amount of homogenate that corresponded to 25 mg (wet weight) of the original placental tissue. The reaction was initiated by adding NAD after all the NADP had been reduced which required 1–2 minutes under the chosen experimental conditions. The reduction of NAD was then fol-

Pulkkinen Martti O and Willman Kalle Acta obst. et gynec. scandinav 46 494, 1967

From the Department of Obstetrics and Gynaecology (Prof L. Rauramo) and the Department of Physiology (Prof K. Hartiala) Turku Finland

HUMAN PLACENTAL STEROID DEPENDENT PYRIDINE NUCLEOTIDE TRANSHYDROGENASE

BY

MARTTI O PULKKINEN AND KALLE WILLMAN

The metabolism of the steroids in the foetoplacental unit has been the subject of intensive study in recent years. The steroids regulate many important metabolic processes within the organism, but the mechanism of their action is largely unknown.

Villee (1963) found that only cells of tissues of the placenta, endometrium, mammary gland and pituitary gland which are target organs of oestrogens contain in their cytoplasms an enzyme that is able to effect direct transfer of hydrogen from nicotinamide adenine dinucleotidephosphate (NADP) to nicotinamide adenine dinucleotide (NAD) This reaction has not been found to take place in the absence of a suitable oestrogen such as 17β-oestradiol. Some studies suggest that oestrogens may in this way increase the energy production in the above-mentioned organs and stimulate a number of synthetic reactions such as those which produce nucleic acids proteins and fats which are of special importance for the proper function of the foetoplacental unit.

Changes occur in the metabolism of oestrogens in many pathological conditions in the foetus and the placenta these are revealed by the variation of the urinary excretion of oestriol (Klopper 1966) It has been considered worth while to study the levels of this enzyme in the placenta in such conditions in the hope that such a study would reveal the factors responsible for the functional disturbances A study has also been made to determine whether other steroids conjugated or unconjugated,

and chorionic gonadotrophin (HCG) promote transhydrogenation. A preliminary report has been published as a congress abstract (1966)

Materials and Methods

The numbers of different types of placentae examined in the study are given in Table I.

Isolation of enzyme from placental tissue

Immediately after its expulsion, the placenta was placed in ice and dissected. A sufficient amount of placental tissue freed from membrane and connective tissue was washed in 0.15 M potassium chloride solution until the wash solution remained clear. The tissue was added in the ratio of one gram to 4 millilitres to a solution of pH 7.0 (I) that was 0.01 M in monopotassium phosphate and 0.005 M in dipotassium ethylenediaminetetra-acetate and contained 20 per cent (v/v) glycerol, and the mixture was homogenized in a Potter-Elvehjem homogenizer. The homogenate was then centrifuged at 57,000×g for 60 minutes. Ammonium sulphate was added to the supernatant until its concentration was 40 per cent of the saturation concentration and the supernatant was left to stand two hours before it was centrifuged at 10 000×g for 30 minutes. The final supernatant contained no enzyme. The precipitate was dissolved in a small volume of a solution (II) of pH 7.0 which was 0.01 M in monopotassium phosphate and 0.005 M in dipotassium ethylenediaminetetra-acetate and contained 50 per cent (v/v) glycerol. The enzyme activity of the solution was determined immediately as follows. A mixture 3.0 ml in volume was prepared from 300 micromoles of Tris buffer solution, 1.5 micromoles of NAD, 6.0 micromoles of sodium dl-isocitrate, 0.075 micromole of NADP, 0.22 micromole of 17β-oestradiol dissolved in 50 microliters of 96 per cent ethanol, 1 m-I.U. of isocitrate dehydrogenase (Sigma), 70 micromoles of manganese sulphate tetrahydrate and an amount of homogenate that corresponded to 125 mg (wet weight) of the original placental tissue. The reaction was initiated by adding NAD after all the NADP had been reduced, which required 1–2 minutes under the chosen experimental conditions. The reduction of NAD was then fol

Pulkkinen Martti O and Willman Kalle Acta obst et gynec scandinav 46, 484, 1967

From the Department of Obstetrics and Gynaecology (Prof L. Rauramo) and the Department of Physiology (Prof K. Hartiala) Turku Finland

HUMAN PLACENTAL STEROID-DEPENDENT PYRIDINE NUCLEOTIDE TRANSHYDROGENASE

BY

MARTTI O. PULKKINEN AND KALLE WILLMAN

The metabolism of the steroids in the foetoplacental unit has been the subject of intensive study in recent years. The steroids regulate many important metabolic processes within the organism but the mechanism of their action is largely unknown.

Villee (*1963*) found that only cells of tissues of the placenta, endometrium mammary gland and pituitary gland, which are target organs of oestrogens, contain in their cytoplasms an enzyme that is able to effect direct transfer of hydrogen from nicotinamide adenine dinucleotidephosphate (NADP) to nicotinamide adenine dinucleotide (NAD) This reaction has not been found to take place in the absence of a suitable oestrogen such as 17β-oestradiol. Some studies suggest that oestrogens may in this way increase the energy production in the above-mentioned organs and stimulate a number of synthetic reactions such as those which produce nucleic acids proteins and fats which are of special importance for the proper function of the foetoplacental unit

Changes occur in the metabolism of oestrogens in many pathological conditions in the foetus and the placenta these are revealed by the variation of the urinary excretion of oestriol (Klopper 1966) It has been considered worth while to study the levels of this enzyme in the placenta in such conditions in the hope that such a study would reveal the factors responsible for the functional disturbances. A study has also been made to determine whether other steroids conjugated or unconjugated,

Table I. Steroid-Dependent Pyridine Nucleotide Transhydrogenase in Normal and Pathological Placentae

Disease	Number of Cases	Mean SDTH Activity
Mild prae-eclampsia	5	5·8
Severe prae-eclampsia		5·5
Chronic hypertension		9
Rh incompatibility		3·4
Neonatal asphyxia	1	3
Calcification of placenta	5	6·9
Macroscopic fat deposits in placenta		2·6
Total	9	5·8 ± 0·4
Normal placentae	9	3·8 ± 53

noted that the SDTH activity is on average higher than normal in mothers suffering from prae-eclampsia and chronic hyper tension and in mothers with calcified placentas, but within the normal range in the mothers whose offspring had been asphyctic, who had rhesus immunization, or in whose placentas there were macroscopic fat deposits.

The in vitro studies revealed that 17β-oestradiol and oestrone and their 3-sulphate conjugates were equally effective inducers of transhydrogenation. Androsterone sulphate promoted the transhydrogenation as effectively as 17β-oestradiol. 17β-oestradiol 17-sulphate was unable to effect the transhydrogenation under the experimental conditions. No transhydrogenation was observed to take place in the presence of dehydroepiandrosterone, dehydroepiandrosterone sulphate pregnandiol and pregnandiol glucuronide. At none of the examined concentrations did human chorionic gonadotrophin have any effect on the reaction promoted by 17β-oestradiol nor did it alone promote the transhydrogenation.

Discussion

The stage of the energy-producing reaction chain which is assumed to be catalyzed by the steroid-dependent pyridine nucleotide transhydrogenase is indicated in Fig. 1

lowed by measuring the absorbance of the mixture at 25 C with a Beckman DU spectrophotometer at 5-minute intervals during the course of 50 minutes The rate of reaction was evaluated from the slope of the linear plot over the period from 10 to 40 minutes The blank was the same mixture except that it contained no steroid All measurements were performed in duplicate The steroid-dependent pyridine nucleotide trans hydrogenase (SDTH) activity is expressed in thousandths of International Unit (m I U) per gram (wet weight) of tissue.

In vitro studies with steroids

The steroids employed in the experiments were oestrone, *oestrone-3 sulphate 17β-oestradiol-3 sulphate 17β*-oestradiol-17 sulphate androsterone androsterone sulphate dehydroepiandros terone dehydroepiandrosterone sulphate, pregnandiol and pregnandiol glucuronide. The composition of the reaction mixture was the same as in the SDTH activity assays except that the 17β-oestradiol was replaced by one of the above steroids. The final concentration of each steroid was 5×10^{-6}M At least 5 replicate experiments were carried out with each steroid.

In vitro studies with human chorionic gonadotrophin

The experimental conditions were the same as in the preceding experiments except that the reaction mixture contained 1 to 1000 units of human chorionic gonadotrophin (Pregnyl) dis solved in water with or without 17β-oestradiol.

Results

The results of the assays of SDTH in placentas from healthy mothers and in those from mothers with various pathological conditions during their pregnancies are collected in Table I The data show that the SDTH levels were higher in the pathological placentas than in normal placentas ($p < 0.01$) It will be

The androgens and their sulphates were donated by Schering A.G and the Pregnyl was from Organon.

Table I. *Steroid-Dependent Pyridine Nucleotide Transhydrogenase in Normal and Pathological Placentae*

Disease	Number of Cases	Mean SDTH Activity
Mild prae-eclampsia	5	5.8
Severe prae-eclampsia	2	5 5
Chronic hypertension	2	9
Rh incompatibility		3 4
Neonatal asphyxia		3 5
Calcification of placenta	5	6 9
Macroscopic fat deposits in placenta		6
Total	9	5 8 ± 0.4
Normal placentae	9	3 8 ± 0 53

noted that the SDTH activity is on average higher than normal in mothers suffering from prae-eclampsia and chronic hypertension and in mothers with calcified placentas but within the normal range in the mothers whose offspring had been asphyctic who had rhesus immunization, or in whose placentas there were macroscopic fat deposits.

The in vitro studies revealed that 17β-oestradiol and oestrone and their 3-sulphate conjugates were equally effective inducers of transhydrogenation. Androsterone sulphate promoted the transhydrogenation as effectively as 17β-oestradiol. 17β-oestradiol 17-sulphate was unable to effect the transhydrogenation under the experimental conditions. No transhydrogenation was observed to take place in the presence of dehydroepiandrosterone, dehydroepiandrosterone sulphate pregnandiol and pregnandiol glucuronide At none of the examined concentrations did human chorionic gonadotrophin have any effect on the reaction promoted by 17β-oestradiol nor did it alone promote the transhydrogenation

Discussion

The stage of the energy-producing reaction chain which is assumed to be catalyzed by the steroid-dependent pyridine nucleotide transhydrogenase is indicated in Fig 1

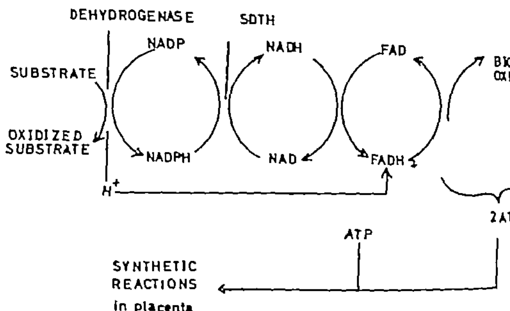


Fig. 1 The stage of hydrogen transfer in cells which is believed to be promoted by steroid-dependent pyridine nucleotide transhydrogenase (SDTH)

FAD—flavin adenine dinucleotide
ADP—adenosine diphosphate
ATP—adenosine triphosphate

This enzyme promotes the direct transfer without the occurrence of the Krebs cycle of hydrogen from NADPH to NAD and further to the cytochrome system. The final product is biologically useful energy stored in ATP (Villee 1963)

As far as we are aware studies have not been previously carried out to determine the activity of the steroid-dependent pyridine nucleotide transhydrogenase in placentae associated with pathological conditions It is known that a vigorous oestrogen synthesis goes on in the foetoplacental unit during pregnancy Obviously one purpose of the oestrogen production is to promote the normal development of the foetus by stimulating necessary syntheses (Tomkins *et al* 1963) Oestrogen synthesis has been found to be suppressed in placentae of mothers suffering from prae-eclampsia and chronic hypertension and in calcified placentae (Klopper 1966) High levels of SDTH were found in placentae in these conditions in the present

study The significance of these high levels cannot be judged with certainty but they may be a sign of a mechanism which tends to maintain adequate energy production when oestrogen synthesis is diminished in the placenta and foetus

It has been demonstrated that primarily oestrogens that possess a hydroxyl or carbonyl group in the otherwise unsubstituted position 17β promote transhydrogenation in placental tissue homogenates (Stempfel, 1964) This was confirmed in the present study by the observation that conjugation of 17β-oestradiol at position 3 did not lead to reduced transhydrogenation, whereas conjugation at position 17 did. Thus conjugation does not always lower the activity of an oestrogen.

Dehydroepiandrosterone and its sulphate are precursors in the biosynthesis of oestrogens (Siiteri *et al* 1966) and it is hence of interest to note that they are unable to promote transhydrogenation.

We have previously found that oestrogen sulphate conjugates may differ from the free oestrogens in their effects on enzyme systems (Pulkkinen *et al* 1966) A similar difference was observed in the case of androsterone and its conjugate in the present study only the conjugate was active. It has been found earlier that testosterone is only about one twentieth as effective a catalyst of the transhydrogenation as 17β-oestradiol (Langer *et al* 1963) and androsterone sulphate For this reason it is more appropriate to define the pyridine nucleotide transhydrogenase as being steroid-dependent rather than oestrogen-sensitive

SUMMARY

There exists an enzyme in the cytoplasm of human placental tissue cells which in the presence of steroid hormones promotes the transfer of a hydrogen atom from reduced nicotinamide adenine dinucleotidephosphate to nicotinamide adenine dinucleotide This reaction is belived to provide energy for synthetic eactions in the placenta

The level of the steroid-dependent pyridine nucleotide transhydrogenase is higher in diseased than in healthy placentae Oestrone 17β-oestradiol and their 3-sulphate conjugates and

androsterone sulphate promote the transhydrogenation to the same extent, but 17β-oestradiol 17-sulphate androsterone dehydroepiandrosterone dehydroepiandrosterone-3 sulphate pregnandiol pregnandiol glucuronide and human chorionic gonadotrophin are without effect

REFERENCES

Klopper A. Research on Steroids 2 63, 1966
Langer L. J and *Engel L. L.* J Biol. Chem. 233 583 1963
Pulkkinen M O and *Willman K.* Acta obst. et gynec. scandinav 45 Suppl. 9 1966
Pulkkinen M O and *Willman K.* Steroids 8 51 1966
Siiteri P K. and *MacDonald P C* J Clin. Endocrinol. 26 751 1966
Stempfel R. S Jr and *Sidbury J B. Jr* J Clin. Endocrinol. 24 367 1964
Tomkins G M and *Maxwell E. S* Ann. Rev Biochem., 32, 677 1963
Villee Cl. A. Modern Trends of Human Record. Physiol 1 81 1963

Received on March 7th, 1967

Nilsson, Carl Axel, Acta obst. et gynec. scandinav. 46, 301, 1967
From the Department of Obstetrics and Gynaecology (Rolf Fåhraeus M.D.) and the Department of Pathology (Gunnar Nethorst Wahdahl M.D.)
Västerås, Sweden

VACUUM-ASPIRATION OF UTERINE CONTENTS IN LEGAL ABORTION AND ALLIED CONDITIONS

BY

CARL-AXEL NILSSON

In 1958 a new method for terminating early pregnancy by aspiration of the uterine contents was published in China (*Wu-Yuan-tai* and *Wu-Hsien chen* 1958). The method was introduced into Russia (*Melks* and *Roze* 1961, *Zubajev* 1962, *Macpanova* 1963) and other East-European countries. It seems to have been extensively used in these countries and the incidence of reported complications is low. Besides language problems, literature from that part of the world is difficult to obtain and study of previous work has essentially been restricted to quotations (*Chalupa* 1964, *Vojta* and *Jirásek* 1965, *Rosenzweig*, 1965).—At this hospital the method has become routine since 1966. It is here somewhat arbitrarily denoted as Vacuum-aspiration (VA).

The principle of intrauterine aspiration using an electrical suction apparatus, however, is not new. It was described more than 30 years ago as a method for obtaining endometrial biopsies (*Lorincz* 1934, *Novak* 1935).

Method

We have tested several suction tubes of varying construction, e.g. straight ones of both hard and semi-flexible material, with the suction opening at the end of the tubes or with one or two openings on the side of them. Nowadays we exclusively use five

androsterone sulphate promote the transhydrogenation to the same extent, but 17β-oestradiol 17-sulphate androsterone, dehydroepiandrosterone dehydroepiandrosterone-3 sulphate, pregnandiol, pregnandiol glucuronide and human chorionic gonadotrophin are without effect.

REFERENCES

Klopper A. Research on Steroids, 2 63 1966
Langer L. J and *Engel L. L.* J Biol Chem. 233 583 1963
Pulkkinen M O and *Willman K* Acta obst. et gynec. scandinav 45 Suppl 9 1966
Pulkkinen M O and Willman K Steroids 8 51 1966
Siiteri P K. and *MacDonald P C* J Clin. Endocrinol. 26 751 1966
Stempfel R. S Jr and *Sidbury J B Jr* J Clin. Endocrinol. 24 367 1964
Tomkins G M., and *Maxwell E. S.* Ann. Rev Biochem 32, 677 1963
Villee Cl A Modern Trends of Human Record. Physiol., 1 81 1963

Received on March 7th, 1967

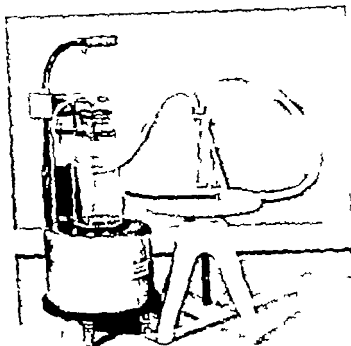


Fig. 2. Suction apparatus. Described in detail in text.

tions. Generally the evacuation can be carried out in the course of a few minutes. With some experience of the method it can be determined when the cavity is empty. The edges of the suction opening, which are blunt, then give approximately the same scraping sensation against the uterine wall as when a blunt curette is used with slight force. If there is any doubt as to the completeness of the evacuation, the uterine cavity is also explored with a blunt curette and/or a small ovum forceps. The operation is always ended by sterile bimanual palpation.

Anaesthesia

When the method was new and the technique was being tested intravenous anaesthesia with short-acting barbiturates was used, chiefly for psychological reasons. As a rule the operation is now

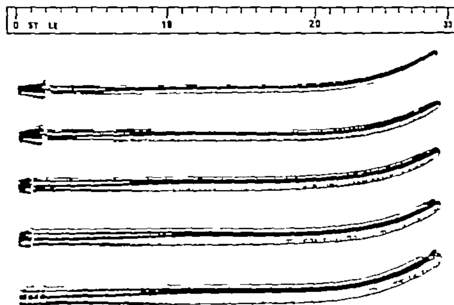


Fig. 1 Suction tubes. Length 30 cm. Further description in text.

metal tubes manufactured by AB Stille-Werner which we have found best suited for the purpose (Fig 1)

The tubes have an outer diameter of 6 8 10 12 and 14 mm and a slight curvature similar to that of ordinary Hegar dilators. Close to the tip there is a suction opening the diameter of which is the same as the inner diameter of the tube 5 7 9 11 and 13 mm respectively The suction tube is connected to a glass bottle by a transparent high-pressure plastic tube. The aspirated material is collected in the glass bottle The bottle is connected to an electric suction apparatus via an additional glass flask, which prevents aspiration of blood and tissue into the electric pump (Fig. 2)

The vulva, vagina and the region of the external os are thoroughly swabbed with benzalkonium chloride solution. A tenaculum forceps is used to steady the portio The cervix is dilated to permit introduction of a suitable suction tube The electric suction apparatus is started and the negative pressure is adjusted to 0 40–0 45 kg/cm^2 Relatively slowly the suction tube is drawn axially in the uterus back and forth between cervix and fundus. At the same time it is rotated systematically in all direc-

Table I. Indications for VA and Type of *Anesthesia*

	Total	Anesthesia		
		General	Local	None
Legal abortion	199	25	174	
Incomplete abortion	77	13	52	12
Infected abortion	12	3	8	1
Missed abortion	7	5	2	
Secondary post partum haemorrhage	7	3	3	1
Hydatidiform mole	1		1	

Table II. *VA in Legal Abortion, Parity and Duration of Pregnancy*

	Total	Duration of pregnancy in weeks									
		7	8	9	10	11	12	13	14	15	16
Nulliparous	40		1	6	8	6	11	6	1	1	
Parous	159	4	3	29	33	34	26	21	6	1	2

In the future we intend to apply the following rules. Nulliparous women may be dilated to maximally Hegar 8 and parous to Hegar 10. We have made exceptions for older women who do not intend to have more children. In a few such cases dilatation to Hegar 14 has been performed, allowing termination up to the 16th week. However, operations after the 13th week have been more difficult, sometimes necessitating the use of an ovum forceps for removal of the foetus. These late cases have been uneventful but our experience is small and we are doubtful whether the method can be recommended for them.

With the rules given above, the range of use of the method will be that shown in Fig. 3. The time limits are chosen to allow for a miscalculation of 1–2 weeks. This, of course, also means that one should always first try the 6 mm suction tube even at the 9th week and the 8 mm tube at the 2th week. It is necessary immediately before operation to ensure by palpation that the size of the uterus corresponds to the stated duration of pregnancy. One might otherwise be faced with severe haemorrhage and thus a situation difficult to control. This examination is of

performed under local anaesthesia 10 ml of 1 % Mepivacaine (Carbocain®) is infiltrated as a paracervical block on either side of the cervix It is combined with an intramuscular injection of Pethidine 50–150 mg and promethazine hydrochloride 25-50 mg, given 30–60 minutes before operation.

In a few cases mainly incomplete abortions when the cervix was sufficiently dilated, the operation was performed without anaesthesia with little discomfort to the patient.

Postoperative care

Directly after operation, 0 25 mg Ergometrine tartrate + 0 125 mg Ergobasine tartrate (Neo-Gynergen®) are injected intramuscularly Stilboestrol tablets 1 mg 4 times daily are given for 5 days. Antibiotics have not been used except for women with signs of infection before VA.

The patients are recommended to rest mostly in bed for 1-2 days and to abstain from hard work for about a week thereafter Until the last 131 legal abortions all women were kept under observation at the clinic for between 1 and 4 days. Since no serious complications were observed during this time we now discharge women with legal abortions after a few hours observation, when home conditions and the mental state are satisfactory A follow-up examination is made after 2–4 weeks.

Material

The successful use of VA in legal abortions has led us to test the method for other indications. The whole series comprises 303 cases Their distribution with respect to indication and type of anaesthesia is presented in Table I

VA in legal abortion Parity and duration of pregnancy in the 199 case of legal abortion are shown in Table II

At what maturity does foetal size limit the use of the method? This is dependant on the degree of dilatation of the cervix. It is thus a matter of judgement, the main risk being overdistension of the isthmus predisposing to habitual abortion.

Table I. *Indications for VA and Type of Anesthesia*

	Total	Anesthesia		
		General	Local	None
Legal abortion	199	25	174	
Incomplete abortion	77	13	52	12
Infected abortion	12	3	8	1
Missed abortion	7	5	2	
Secondary post partum haemorrhage	7	3	3	1
Hydatidiform mole	1		1	

Table II. *VA in Legal Abortion. Parity and Duration of Pregnancy*

	Total	Duration of pregnancy in weeks									
		7	8	9	10	11	12	13	14	15	16
Nulliparous	40		1	6	8	6	11	6	1	1	
Parous	159	4	3	29	33	34	26	21	6	1	2

In the future we intend to apply the following rules. Nulliparous women may be dilated to maximally Hegar 8 and parous to Hegar 10. We have made exceptions for older women who do not intend to have more children. In a few such cases dilatation to Hegar 14 has been performed, allowing termination up to the 16th week. However operations after the 13th week have been more difficult sometimes necessitating the use of an ovum forceps for removal of the foetus. These late cases have been uneventful but our experience is small and we are doubtful whether the method can be recommended for them.

With the rules given above the range of use of the method will be that shown in Fig. 3. The time limits are chosen to allow for a miscalculation of 1 2 weeks. This, of course also means that one should always first try the 6 mm suction tube even at the 9th week and the 8 mm tube at the 2th week. It is necessary immediately before operation to ensure by palpation that the size of the uterus corresponds to the stated duration of pregnancy. One might otherwise be faced with severe haemorrhage and thus a situation difficult to control. This examination is of

DURATION OF PREGNANCY IN WEEKS	DILATATION REQUIRED	RANGE OF USE	
		PAROUS	NULLIPAROUS
7	HEGAR 6		
8			
9	HEGAR 8		
10			
11			
12	HEGAR 10		
13			

Fig. 3. VA in legal abortion. Recommended range of use.

course also essential in order to gain an accurate conception of the position of the uterine body.

VA in incomplete abortion. The method was used in 77 patients. Seven of these were legal abortions induced by extraamniotic injections of hypertonic saline (*Svane* 1959). The rest were spontaneous abortions. The operations were invariably easy to carry out. However, in these cases the whole placenta or a large part of it may be aspirated into the suction opening at once and fasten there. The suction tube must then be withdrawn from the uterus and cleaned after which the operation can be continued.

Nevertheless, for this indication VA does not generally seem to have any advantage over conventional methods, except when one encounters a case in which the bleeding is severe, and it is an advantage to be able to empty the uterus immediately without anaesthesia. Frequently these women have been taking fluids (thirst due to pre-shock), which is a relative contraindication

to anaesthesia. In such cases VA may be the method of choice since it causes less pain and discomfort than conventional instrumental evacuation.

VA in infected abortion. By "infected" are meant cases in which the oral temperature before evacuation exceeded 37.7° C (rectal temperature > 38.0° C). Criminal interference is known or suspected in most cases. Only 2 of our 12 patients had a temperature above 38.7° C and other signs of infection were also mild. The object of testing the method was the possibility of running less risk of spreading the infection to the tubes and parametrium as well as to blood and lymph vessels as the uterine contents were aspirated from the cavity. The postoperative course was uncomplicated in all 12 cases.

VA in missed abortion. In this condition we have for several years used high doses of ethinyl oestradiol and/or extraamniotic injection of hypertonic saline to induce abortion (*Bengtsson* 1962, *Bengtsson* and *Falk* 1964). The scheme has been mostly successful.

The 7 cases presented correspond to the accepted definition of missed abortion with suspected foetal death 8 weeks or more before intervention (*Litzenberg*, 1921). They did not respond to oestrogen therapy. VA was done without complications. In missed abortion, haemorrhage is sometimes profuse without any previously demonstrable coagulation defect. This was the reason for testing the new method, which is consistently accompanied by surprisingly little bleeding.

VA in secondary post-partum haemorrhage. The method was used in 6 women who were readmitted between 3 and 6 weeks after parturition for haemorrhage. The deliveries had been uncomplicated and no defects were observed in the placentae. Nevertheless, on VA small pieces of tissue were easily recovered. Microscopical examination showed degenerated placental tissue. The postoperative course was uneventful.

A 7th woman had high fever besides the bleeding.

M.S. 29.11.66. Para-1, gravida-1, aged 23, unmarried. Spontaneous twin

delivery 4 weeks before term. Rupture of the membranes 7 1/2 hours before delivery of the second twin. Blood loss 450 ml. Placenta and membranes without obvious defects. Slight fever not exceeding 38.0 C, for 3 days in the puerperium. Rather foul discharge. No antibiotics administered. Discharged after 7 days without fever abnormal bleeding or other symptoms.—Readmitted 6 days later in pre-shock. Temperature 39.0 C–40.5 C. Severe rigors. Brisk, fresh bleeding. Uterus the size of a 14–16 week pregnancy soft, somewhat tender. Antibiotic therapy instituted at once. *Streptomycin* 1g×2 for 5 days. Penicillin 2.2 mil IU×2 for 8 days.—Two hours after admission the uterus was emptied with VA without anaesthesia. Contents: Rather abundant masses of ill-smelling dark blood clots and small pieces of tissue. Unfortunately no cultures taken. Microscopy: Necrotic placenta and decidua with signs of severe inflammation. There was also a fragment of muscle tissue.—During the following 6 hours temperature 39.5 C–40.5 C, rigors and a tendency to hypotension (septic?). Blood-pressure at the lowest 70/50 and urinary out-put never below 25 ml/2 hours. After VA only sparse bleeding and temperature quite normal within 36 hours. Consequent course uncomplicated. Hysterosalpingography (HSG) planned but returned pregnant 5 months later.

VA in hydatidiform mole. One case is described in which a hydatidiform mole was evacuated by VA with minimal bleeding (*Vojta* and *Jirásek* 1965). We have recently used the method in an advanced case of hydatidiform mole with dead foetus.

L.H. 24/67. Gravida-I, aged 17. Admitted in the 17th pregnancy week because of severe oedema blood-pressure 140/90–160/110 mmHg and proteinuria 2.5–7.0 ‰. Uterus far too big for the 17th week with fundus 1 cm above the umbilicus. Immunological HCG-determinations in urine 2.4–3.2 mil. IU. Strong suspicion of hydatidiform mole but X-ray revealed a foetus, the size of which corresponded to the stated duration of pregnancy. Foetal movements and positive FEcg in the 20th week. Constant severe proteinuria and oedema. Anemia with Hgb between 8 and 9 g/100 ml. Never any bleeding. Foetal movements disappeared between the 22nd and the 24th week. No foetal sounds. X-ray in the 26th week showed that the size of the foetus had diminished approximately 15 % since the 21st week. Fundus now 3 cm above the umbilicus.—VA performed under local anaesthesia. No dilatation as the cervix was found to be open for Hegar 15. The uterus was emptied partly of molar tissue and partly of degenerate placenta. The macerated foetus had to be removed with an ovum forceps. Total tissue weight 1400 g. Total fluid evacuated 1000 ml of which approximately 300–400 ml was discoloured amniotic fluid and the rest blood. Microscopy: Placental tissue with extensive molar degeneration. Postoperative course uncomplicated. HCG negative within 3 weeks. Histaminase determination normal after 8 weeks (Willert).

Complications

Since the observation period does not exceed one year in any of the present cases, an account must be confined to the early complications (Table III)

Table III Complications *Denotes "the 131 Last Cases Not Observed in Hospital for More Than a Few Hours Denotes "Presumably Drug Fever Denotes "Same case —The Indication for Blood Transfusion was Bleeding Before V A in All Cases Except the Hydatidiform Mole*

			Legal abortion	Incomplete abortion	Infected abortion	Missed abortion	Secondary postpartum haemorrhage	Hydatidiform mole
Total			199	77	12	7	7	1
Oral temp after operation	37 2° C	2	1	2				
	> 37 7° C	1					1	
Bleeding necessitating blood transfusion				6			1	1
Salpingitis			2					
Incomplete evacuation			2	1				

In 3 cases the oral temperature during the postoperative observation period in hospital exceeded 37 2 C on two consecutive readings. Temperature over 37 7 C was only observed in the woman with puerperal sepsis described in detail above.

One patient who underwent legal abortion exhibited a typical drug rash during the day after operation, possibly caused by the local anaesthetic She also had slight fever and is one of the cases mentioned above The rash and fever disappeared upon treatment with ACTH 60 IU for two days

Bleeding during and after VA was consistently inappreciable and in contrast to our experience of conventional instrumental evacuation for legal abortion when bleeding may be profuse particularly in pregnancies after the 10th week.—Blood transfusions were given to 8 women. Only in one case—the hydatidi-

delivery 4 weeks before term. Rupture of the membranes 7 1/2 hours before delivery of the second twin. Blood loss 450 ml. Placenta and membranes without obvious defects. Slight fever not exceeding 38.0 C, for 3 days in the puerperium. Rather foul discharge. No antibiotics administered. Discharged after 7 days without fever, abnormal bleeding or other symptoms.—Readmitted 6 days later in pre-shock. Temperature 39.0 C–40.5 C. Severe rigors. Brisk fresh bleeding. Uterus the size of a 14–16 week pregnancy, soft, somewhat tender. Antibiotic therapy instituted at once. Streptomycin 1g×2 for 5 days, Penicillin 2.2 mil IU×2 for 8 days.—Two hours after admission the uterus was emptied with VA *without anaesthesia*. *Contents*: Rather abundant masses of ill-smelling dark blood clots and small pieces of tissue. Unfortunately no cultures taken. Microscopy: Necrotic placenta and decidua with signs of severe inflammation. There was also a fragment of muscle tissue.—During the following 6 hours temperature 39.5° C–40.5 C, rigors and a tendency to hypotension (septic?). Blood-pressure at the lowest 70/50 and urinary out-put never below 25 ml/2 hours. After VA only sparse bleeding and temperature quite normal within 36 hours. Consequent course uncomplicated. Hysterosalpingography (HSG) planned but returned pregnant 5 months later.

VA in hydatidiform mole. One case is described in which a hydatidiform mole was evacuated by VA with minimal bleeding (*Vojta* and *Jirdsek* 1965). We have recently used the method in an advanced case of hydatidiform mole with dead foetus.

L.H. 24/67. Gravida-I, aged 17. Admitted in the 17th pregnancy week because of severe oedema, blood-pressure 140/90–160/110 mmHg and proteinuria 2.5–7.0 ‰. Uterus far too big for the 17th week with fundus 1 cm above the umbilicus. *Immunological HCG-determinations in urine* 2.4–3.2 mil. IU. Strong suspicion of hydatidiform mole but X-ray revealed a foetus, the size of which corresponded to the stated duration of pregnancy. Foetal movements and positive FEcg in the 20th week. Constant severe *proteinuria* and oedema. Anemia with Hgb between 8 and 9 g/100 ml. Never any bleeding. Foetal movements disappeared between the 22nd and the 24th week. No foetal sounds. X-ray in the 26th week showed that the size of the foetus had diminished approximately 15 % since the 21st week. Fundus now 3 cm above the umbilicus.—VA performed under local anaesthesia. No dilatation as the cervix was found to be open for Hegar 15. The uterus was emptied partly of molar tissue and partly of degenerate placenta. The macerated foetus had to be removed with an ovum forceps. Total tissue weight: 1400 g. Total fluid evacuated 1000 ml of which approximately 300–400 ml was discoloured amniotic fluid and the rest blood. Microscopy: Placental tissue with extensive molar degeneration. Postoperative course uncomplicated. HCG negative within 3 weeks. Histaminase determination normal after 8 weeks (Willert).

Complications

Since the observation period does not exceed one year in any of the present cases, an account must be confined to the early complications (Table III)

Table III. Complications. Denotes "*the 131 Last Cases Not Observed in Hospital for More Than a Few Hours* Denotes *Presumably Drug Fever* Denotes "*Same case* —*The Indication for Blood Transfusion was Bleeding Before VA in All Cases Except the Hydatidiform Mole*

			Legal abortion	Incomplete abortion	Infected abortion	Missed abortion	Secondary postpartum haemorrhage	Hydatidiform mole
Total			199	77	12	7	7	1
Oral temp after operation	37.2° C	2	1	2				
	37.7° C	1					1	
Bleeding necessitating blood transfusion				6			1	1
Salpingitis			2					
Incomplete evacuation			2	1				

In 3 cases the oral temperature during the postoperative observation period in hospital exceeded 37.2 C on two consecutive readings Temperature over 37.7 C was only observed in the woman with puerperal sepsis described in detail above.

One patient who underwent legal abortion exhibited a typical drug rash during the day after operation, possibly caused by the local anaesthetic She also had slight fever and is one of the cases mentioned above The rash and fever disappeared upon treatment with ACTH, 60 IU for two days.

Bleeding during and after VA was consistently inappreciable and in contrast to our experience of conventional instrumental evacuation for legal abortion, when bleeding may be profuse particularly in pregnancies after the 10th week —Blood transfusions were given to 8 women. Only in one case—the hydatidi-

[illegible]

form mole—was the indication for transfusion bleeding during or after VA

Two women who had undergone legal abortion and one woman with incomplete abortion were readmitted because of bleeding 4–7 weeks after VA. On renewed curettage a few small pieces of tissue were recovered which on microscopical examination proved to be necrotic placenta.

Clinical suspicion of salpingitis was present in 7 cases. Three of these women presented the following symptoms Slight pain and tenderness moderately elevated ESR no fever no definitive enlargement of the uterine appendages on palpation. Laparoscopy was performed without delay In one patient it revealed sparse bleeding from one ovary (ovulation?) in another retrograde uterine bleeding through the tubes. In the third case nothing noteworthy was observed at all —In two women adnexal enlargement was noticed after VA. In one of these women laparoscopy disclosed a small cyst, approximately 2×2×2 cm in the ovary but there were no signs of salpingo-oophoritis. In the other laparoscopy disclosed an unruptured tubal pregnancy 3 weeks after VA for incomplete abortion (no microscopy of evacuated material!) —In two women the clinical signs of salphingitis were thought to be so typical that unfortunately laparoscopy was not performed They received the usual treatment in hospital for about two weeks HSG 2 months later was quite normal with free passage through the tubes

In 60 consecutive cases of legal abortion all the material evacuated was kept for microscopical examination. Muscle fibres from the uterine wall were observed in two cases. Both women had normal mentruation without pain within 6 weeks. HSG revealed no sign of intrauterine adhesions and there was free passage through the tubes An intrauterine contraceptive device (IUD) Lippes loop was inserted in these patients as well as 66 other women. These patients were not consecutive cases but selected only in the sense that IUD was thought to be the appropriate contraceptive method At the time of insertion the uterine cavity was thoroughly probed. Adhesions could not be found in any case This method, though, is admittedly inadequate to detect smaller adhesions.

Discussion

VA as a method for evacuating the uterine cavity seems to be characterized by few and unimportant immediate complications. The cervix need not be dilated as much as for conventional curettage and the risk for cervico-isthmical incompetence should therefore be less. The operation is easy to perform and bleeding is usually inappreciable. Several authors have measured the bleeding and found it significantly less than in curettage. (*Cernucha* 1963 *Chalupa* 1964 *Vladov et al.* 1965)

In the original article one perforation is reported in 300 cases. It was presumed to be a result of the dilatation (*Wu-Yuan tai* and *Wu Hsien-chen* 1958) However the risk of perforating the uterus is slight Thus a total of 14 050 VA without perforation were described by different authors at the XI Gynecological Congress in Moscow 1963 (*Chalupa* 1964) Nevertheless, this remains one of the most serious risks. Obviously if the surgeon does not notice the perforation at once, severe visceral damage may arise. For this reason it might be recommended that local anaesthesia be used to the greatest possible extent This is because one is then forced to proceed cautiously otherwise the woman will experience discomfort or even pain. Moreover if perforation occurs the patient ought to react by severe pain with the traction on intestine or omentum. The negative pressure can then be released before the suction tube is withdrawn from the uterus.– We also believe that the method should be used with special care in infected abortion when criminal interference is suspected and the uterus may already be perforated.

Microscopical examination of the evacuated material sometimes discloses muscle fibres from the uterine wall. In our series such fragments were found in 2 (3.3 per cent) out of 60 consecutive cases The reported incidence varies between 0 per cent (*Vladov et al.* 1965) 1 per cent (*Chalupa* 1964) 1.5 per cent (*Melks* 1963) and 20 per cent (*Cernucha* 1963) This variation might only reveal the different numbers of microscopical sections examined. It is almost an impossibility to scrutinize the abundant material in serial sections.—A factor of clinical importance is that the differences could be a function of the nega-

the pressure used. This opinion is somewhat contradicted by the facts that Vladov et al worked at −0.5 to −1.0 kg/cm² and Chalupa at −0.4 kg/cm². We initially used a negative pressure of 0.7 kg/cm². Nowadays we never go under −0.45 kg/cm². We also believe that the edges of the suction opening should be very blunt to avoid damage.

Muscle fragments may also be produced by conventional evacuation, even if a blunt curette is used. The risk of intrauterine adhesions evidently exists and presumably not only in cases where muscle fragments are observed. We have neither seen any case of amenorrhoea after VA nor found such complications reported in the literature. We believe that the new method is not traumatic to the uterine mucosa and submucosa but only further clinical experience and long term follow-up can settle this question.

There must be a risk of ascending infection, salpingitis and eventually sterility, especially if there is a clinically silent gonococcal infection in the cervix at the time of the operation. As a matter of fact, venereal disease can be expected with increased frequency among women that undergo legal abortion in this country as part of the group thus selected is characterized by high promiscuity. In the future we will make it a routine to exclude gonococcal infection by cultures from cervix, urethra and rectum a few days before VA, *i.e.* in time to postpone the operation until treatment has been instituted.

Endometritis and parametritis have been observed after VA (*Chalupa* 1964, *Vladov et al.* 1965). However, these conditions are not very well defined and the authors do not give any information as to their diagnostic criteria. Salpingitis is reported in 2 out of 100 cases (*Chalupa* 1964) and 1 out of 302 cases (*Vladov et al.* 1965). It has been stated that the diagnosis of adnexal inflammation can often not be fool-proof without laparoscopy (*Sövall* 1962 and 1964, *Jacobson* 1964). The presented 7 cases are good illustrations of this.

In conventional curettage small particles and fluid from the uterine contents can be introduced into the maternal circulation. In VA this may possibly be counteracted by the relatively strong force of suction. Theoretically, this might imply advantages in

infected abortion, hydatidiform mole and legal abortion in Rh-negative women (*Hrubisko* 1964) Unfortunately this may prove to be a too mechanistic view especially of the immunization process.

If this operation for legal abortions can be carried out as an out-patient procedure without additional risks this would be of great advantage, as we are constantly faced with a severe shortage of hospital beds, nurses and other attendants. It could also be advantageous to many of these patients, who are mentally unstable. Confrontations with other patients such as sterility cases, are not always easily prevented in an overcrowded ward. Furthermore, the trying time of waiting for operation after the decision of the Abortion Consulting Board could be reduced almost to nil.

SUMMARY

A new method for emptying the uterine cavity by suction, originally described in China in 1958 for termination of early pregnancy has been used in totally 303 cases. The method is technically simple and associated with few immediate complications. The cervix need not be dilated as much as in conventional curettage and bleeding is generally minimal. It is questionable whether the method is more traumatic to the uterine mucosa submucosa and muscular coat than curettage The risk of uterine perforation is slight but potentially serious

The method appears to be useful in interruption of early pregnancy as w ll as in evacuation of hydatidiform mole It may be ad antageous in infected abortion, missed abortion and in incomplet bortion as well as secondary post-partum haemorrhage when bleeding is profuse and necessitates immediate intervention without anaesthesia.

Acknowledgements

I am indepted t Dr Gunnar Nathorst Windahl who has carried ut the histological examinations and to Dr Peter Lee for invaluable advice and criticism.

tive pressure used. This opinion is somewhat contradicted by the facts that Vladov et al worked at −0.5 to −1.0 kg/cm² and Chalupa at −0.4 kg/cm². We initially used a negative pressure of 0.7 kg/cm². Nowadays we never go under −0.45 kg/cm². We also believe that the edges of the suction opening should be very blunt to avoid damage.

Muscle fragments may also be produced by conventional evacuation, even if a blunt curette is used. The risk of intrauterine adhesions evidently exists and presumably not only in cases where muscle fragments are observed. We have neither seen any case of amenorrhoea after VA, nor found such complications reported in the literature. We believe that the new method is not traumatic to the uterine mucosa and submucosa but only further clinical experience and long term follow-up can settle this question.

There must be a risk of ascending infection, salpingitis and eventually sterility, especially if there is a clinically silent gonococcal infection in the cervix at the time of the operation. As a matter of fact, venereal disease can be expected with increased frequency among women that undergo legal abortion in this country as part of the group thus selected is characterized by high promiscuity. In the future we will make it a routine to exclude gonococcal infection by cultures from cervix, urethra and rectum a few days before VA, *i.e.* in time to postpone the operation until treatment has been instituted.

Endometritis and parametritis have been observed after VA (*Chalupa* 1964, *Vladov et al.* 1965). However these conditions are not very well defined and the authors do not give any information as to their diagnostic criteria. Salpingitis is reported in 2 out of 100 cases (*Chalupa* 1964) and 1 out of 302 cases (*Vladov et al.* 1965). It has been stated that the diagnosis of adnexal inflammation can often not be fool-proof without laparoscopy (*Sövall* 1962 and 1964, *Jacobson* 1964). The presented 7 cases are good illustrations of this.

In conventional curettage small particles and fluid from the uterine contents can be introduced into the maternal circulation. In VA this may possibly be counteracted by the relatively strong force of suction. Theoretically this might imply advantages in

infected abortion, hydatidiform mole and legal abortion in Rh-negative women (*Hrubisko* 1964) Unfortunately this may prove to be a too mechanistic view especially of the immunization process

If this operation for legal abortions can be carried out as an out-patient procedure without additional risks this would be of great advantage, as we are constantly faced with a severe shortage of hospital beds, nurses and other attendants. It could also be advantageous to many of these patients, who are mentally unstable. Confrontations with other patients such as sterility cases, are not always easily prevented in an overcrowded ward. Furthermore the trying time of waiting for operation after the decision of the Abortion Consulting Board could be reduced almost to nil.

SUMMARY

A new method for emptying the uterine cavity by suction, originally described in China in 1958 for termination of early pregnancy has been used in totally 303 cases. The method is technically simple and associated with few immediate complications. The cervix need not be dilated as much as in conventional curettage and bleeding is generally minimal. It is questionable whether the method is more traumatic to the uterine mucosa submucosa and muscular coat than curettage The risk of uterine perforation is slight but potentially serious

The method appears to be useful in interruption of early pregnancy as well as in evacuation of hydatidiform mole It may be advantageous in infected abortion, missed abortion and in incomplete abortion as well as secondary post-partum haemorrhage when bleeding is profuse and necessitates immediate intervention without anaesthesia.

Acknowledgements

I am indepted to Dr Gunnar Nathorst Wandahl, who has carried out the histological examinations and to Dr Peter Lee for invaluable ad ice and criticism.

Authors address. Kvinnokliniken, Regionsjukhuset, LINKÖPING Sweden

REFERENCES

Bengtsson L. Ph. Lancet *1* 339 1962
Bengtsson L. Ph. and *Falk V* Obstetrik & Gynekologi, ? 77 1964
Cernucha J A. Sovremennyje metody issledovanija i lecenija v akuserstve i ginekologii Moscow 1963 Quoted by Chalupa
Chalupa M Zbl. Gynäk., *86* 1803 1964
Cislo M Novosad K. and *Reszczyński A.* Zbl. Gynäk., *88* 156, 1966
Hrubliko O Mergancová D Bruchál D and *Vlerik J* Cd. gynaek. 29/43 90 1964 Quoted by Chalupa
Jacobson L. Acta obst. et gynec. scandinav. *43* 160 1964
Kiss O Geburtsh. u. Frauenheilk., *26* 38 1966
Litzenberg, J C. Amer J Obstet. Gynec *1* 475 1921
Löriner B. München. Med. Wchnschr *81* 215 1934
Macpanova O D XI All Union Congress Gyn., Moscow 1963. Quoted by Chalupa
Melks E I and *Ro e L. V* Novoe v akuserstve i ginekologii Riga 1961 Quoted by Chalupa
Novak E. J.A.M.A., *104* 1947 1935
Rosenzweig, E. Minerva Ginec. *17* 731 1965
Sjövall A. Kungl. Fysiogr Sällsk. *I Lund förhandl. Bd 32 Nr 11* 1962
– Proc. first internat. symposium gyn. celioscopy p. 329 1964 Palermo 1964
Svane H Ugeskr laeg *121* 717 1959
Vladov E. Ivanov I., Angelov A. and *Rakilovska I* Gynaecologia, *159* 54 1965
Vojta M and *Jirásek J* Zbl. Gynäk., *87* 1225 1965
Zubejev A. V Voprosy akus. i ginek. pomosci, *25* 1962. Quoted by Vojta and Jirásek
Wu-Yuan-tai and *Wu Hsien-chen* Chin J Obstet. Gynec., *6/5* 447 1958 Abstract in Excerpta Med. Sect. X, *12* 244 1959

Received on Jan. 18th, 1967

Ylöstalo, Pekka, Russila, Jaakko and Eekonen, Ahti. Acta obst. et gynec. scandinav. 46, 515, 1967
From the Department of Gynaecology and Obstetrics (S. Lähteenmäki M.D.)
Kuopio Central Hospital, Finland

HEPATOBILIARY FUNCTION IN PUERPERIUM AFTER NORMAL PREGNANCY AND TOXAEMIA OF LATE PREGNANCY WITH SPECIAL REFERENCE TO THE RADIOACTIVE ROSE BENGAL TEST

BY

PEKKA YLÖSTALO, JAAKKO RUSSILA AND AHTI EEKONEN

Liver function tests during normal pregnancy often show abnormal values; a comprehensive report on these tests has recently been published by *Haemmerli* (1966). A considerable number of these results show raised alkaline phosphatase (*Wetstone et al.* 1958, *McNair* and *Jaynes* 1960, *Kubli* 1961, *Dass* and *Bhagwanani* 1964). Pathological values in thymol turbidity test were noted in 0–15 per cent of the cases examined (*Christhilf* and *Bonsnes* 1950, *Wetstone et al.* 1958, *McNair* and *Jaynes* 1960, *Friedberg* 1962). The bromsulphthalein test was found to be normal (*Christhilf* and *Bonsnes* 1950, *Brewer* and *Hjelte* 1965) and pathological in only a small number of cases (*Friedberg* 1962). *Cavalli* (1964) reported that bromsulphthalein clearance was reduced during pregnancy. Total cholesterol increases, in most patients, towards the end of pregnancy (*Wetstone et al.* 1958, *McNair* and *Jaynes* 1960), while serum transaminases usually remain normal. Total serum bilirubin in the large series of 564 pregnant women reported by *McNair* and *Jaynes* (1960) exceeded 1 mg % in only 4 per cent of the patients, while none were over 2 mg %. The histological picture of the liver is normal during a normal pregnancy (*Ingerslev* and *Teilum* 1945 (1), *Antia et al.* 1958). The relative blood flow of the liver is reduced during pregnancy, while the absolute

flow remains unchanged (*Munnell* and *Taylor* 1947)

The pathological liver function values during pregnancy have usually been attributed to serum protein changes produced by pregnancy and to placental action. *Sherlock* (1963) states that normal pregnancy causes no liver lesions, and this opinion is supported by the rapid postpartum return to normal of the tests (*McNair* and *Jaynes* 1960)

The function of the gallbladder is disturbed during pregnancy and disorders have been attributed to stasis of the bile ducts (*Potter*, 1936) spasm of Oddi's sphincter (*Gerdes* and *Boyden* 1938) atony (*Naegeli*, 1929) and general motility disorders (*Westphal*, 1923) Visualization of gallbladder on radiography during pregnancy is more difficult than in the non-pregnant subject (*Unnérus* 1964)

In patients with toxaemia of pregnancy changes are usually more marked this is true especially of the thymol turbidity and bromsulphthalein tests (*Friedberg*, 1962 *Brewer* and *Hjelte* 1965) and of bromsulphthalein clearance (*Cavalli* 1964) Changes in serum transaminases also are more frequent among toxaemic patients, even if no significant correlation to the degree of severity of the toxaemia has been established (*Borglin* 1959 *Crisp et al* 1959 *Ojanen* 1960 *Dass* and *Bhagwanani* 1964 *Maqueo et al* 1964) Alkaline phosphatase again is not on an average elevated more than in a normal pregnancy (*Dass* and *Bhagwanani* 1964) *Antia et al* (1958) and *Dass* and *Bhagwanani (1964 II)* found only minor histological changes in the liver in pre-eclampsia and definite changes in eclampsia, whereas *Ingerslev* and *Tellum* (1945 II) saw changes only with the latter

The purpose of the present investigation was to compare the radioactive Rose Bengal test (RB) with the other liver function tests in puerperium following normal pregnancy and toxaemia. *Nordyke* and *Blahd* (1959) and *Dyrbye* and *Christensen* (1960) consider the test as sensitive as the bromsulphthalein test in addition the test yields information on hepatic excretion. As far as is known, no results on the radioactive rose bengal test in connection with pregnancy have been reported previously in the literature In view of the load produced by irradiation the first tests were made on the second postpartum day

Material and methods

The series consisted of 15 normal pregnant women and 15 with toxaemia of late pregnancy all treated at the Kuopio Central Hospital Department of Obstetrics The toxaemias were classified as recommended by the American Committee of Maternal Welfare. The toxaemia group consisted of 7 patients with mild pre-eclampsia and 8 with severe pre-eclampsia.

On the second or third postpartum day (Test I) the patient s blood was tested for serum alkaline phosphatase icterus index, serum proteins thymol turbidity mercuric chloride and zinc sulphate Weltmann coagulation band glutamic-oxaloacetic transaminase (SGOT) and glutamic-pyruvic transaminase in the serum (SGPT) In addition, a bromsulphthalein test (BSP) and radioactive Rose Bengal test (RB) were carried out. These same tests were repeated 6 weeks later (Test II)

The BSP test was effected by giving the patient, who had fasted overnight 5 mg of dye per kg of body weight and determining the content in blood after 60 minutes (Kessel 1956) A content of 0.25 mg % was considered the upper limit of the normal range

In the radioactive rose bengal test the examination agent used was Rose Bengal dye (tetraiodo-tetrachlorfluoresceín) labelled with I 131 After intravenous injection the dye is removed from the blood into the parenchymal cells of the liver and excreted from the liver by bile ducts into the intestine (*Taplin et al.* 1959)

The patient who had fasted overnight, was given 15–20 μCi of RB by intra enous injection. Changes in blood activity were observed by one detector directed at the head, while another was directed at the intestinal region and recorded the excretion of RB into the intestine The output of both detectors was connected to rate meters (adjustments measurement range 10 c/min time constant 30 sec.) and results were obtained from a dual recorder (paper speed 1 5 mm/min.)

The relationship of the 5 min. and 20 min readings was used for analysis of the blood curve, as indicator of parenchymal function (upper limit for the normal range 55 per cent) The

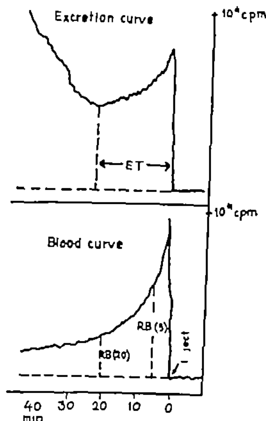


Fig. 1 Interpretation of the curves obtained from Rose Bengal measurements. Model curves.
Excretion curve (measured at the navel) Excretion time (ET) is the lapse of time from moment of injection to the minimum point of the curve. In this curve ET is 25 min.
Blood curve (measured at head) RB(5) and RB(20) are the heights of the curve at 5 and 20 min. The blood value is the percentage ratio of these heights $\frac{RB(20)}{RB(5)} \times 100$ % The blood value of this curve is 45 per cent

numerical index taken for the rate of excretion was the lapse of time from injection to the minimum level of excretion curve (Fig 1)

To inhibit accumulation in the thyroid of the free or liberated iodine possibly present in the RB the patients were given Lugol s solution prior to the examination and to stimulate bile secretion, 2 dl of milk 30 minutes after the injection.

Table I. *Incidence of Pathological Test Results*

	Alkaline Phosphatase	Icterus Index	Thymol Turbidity	Mercuric Chloride test	Weltmann Coagulation Band	SGOT	SGPT	RB Blood Values	BSP	Zinc Sulphate Test
Controls										
Test I 15 patients	12	0	1	1	2	2	2	6	4	0
Test II 11 patients	1	0	0	0	2	0	0	2		0
Toxaemia										
Test I 15 patients	13	1	0	5	3	2	1	7	9	1
Test II 15 patients	0	1	4	1	4	0	1	2	2	0

Results

Eleven of the subjects with normal pregnancy and all 15 of those with toxaemia came for the follow-up examination after 6 weeks. Since the series is so small, the toxaemic groups are combined. The incidence of pathological test results can be seen from Table 1. The change in serum proteins calculated as a mean for the 11 normal pregnancies, was from 6.1 to 7.4 and for the 11 toxaemic patients from 6.1 to 7.2 gm %.

Fig. 2 illustrates the change in the blood values of RB test in the 6 weeks before the follow-up examination. A declining trend is detectable although the differences between Tests I and II were not statistically significant $(0.05 > p > 0.01)$.

Fig. 3 shows a comparison of BSP and RB. Of the results of Test I 11 out of 30 (37 per cent) were contradictory as were 5 out of 26 (19 per cent) of the results of Test II.

For alkaline phosphatase there was no significant difference

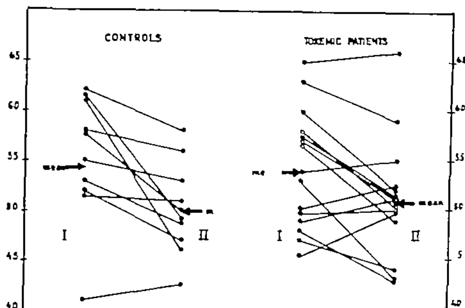
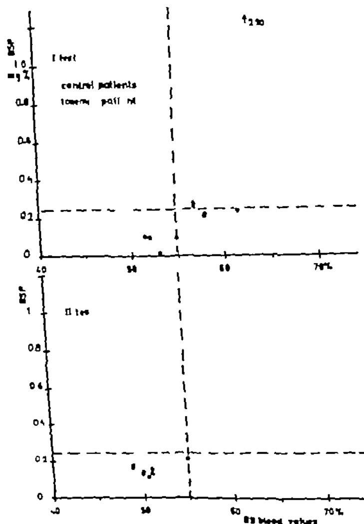


Fig. 2. Change in the blood values of the Rose Bengal test in the 6 post partum weeks.

between the toxaemic patients and the control group (with normal pregnancies) in either test. In Test I the mean value of both groups was 3 6 Bessey-Lowry (B L) units (upper limit for the normal range 2.3) while in Test II the mean for the control group was 1 8 and that for the toxaemic group 1 6 B L units. The mean excretion time in rose bengal test was in Test I 54 minutes for both groups while in Test II the mean for the control group was 23 min. and for the toxaemic patients 24 min. Both in alkaline phosphatase and in RB excretion times the values of Tests I and II show highly significant differences. A highly significant positive correlation was noted between the alkaline phosphatase and RB excretion tests (Fig 4)

Discussion and conclusions

Icterus index, flocculation tests and serum transaminases gave a few pathological values primarily in the toxaemic group but



F g 3 C mpari n f bromsulphthalein test results and ose bengal blood values The dotted lines indicate the upper lim of the normal range In the left lower quadrant both tests were normal and in the right upper quadran pathological I the lef upper quadrant the RB was normal and PSP pathological, and in the right lower quadrant vice versa.

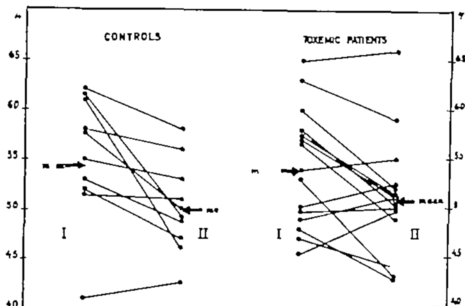


Fig 2 Change in the blood values of the Rose Bengal test in the 6 post partum weeks.

between the toxaemic patients and the control group (with normal pregnancies) in either test. In Test I the mean value of both groups was 3 6 Bessey-Lowry (B L) units (upper limit for the normal range 2.3) while in Test II the mean for the control group was 1 8 and that for the toxaemic group 1 6 B L units. The mean excretion time in rose bengal test was in Test I 54 minutes for both groups while in Test II the mean for the control group was 23 min and for the toxaemic patients 24 min. Both in alkaline phosphatase and in RB excretion times, the values of Tests I and II show highly significant differences. A highly significant positive correlation was noted between the alkaline phosphatase and RB excretion tests (Fig 4)

Discussion and conclusions

Icterus index flocculation tests and serum transaminases gave a few pathological values primarily in the toxaemic group but

the reliability of the RB test. The normalization in the blood values of RB test in 6 weeks may be attributable to the normalization of the relative blood flow of the liver

Extension of the excretion time in RB test immediately post partum implies that bile excretion into the intestine is slowed. The positive correlation noted between alkaline phosphatase and excretion time suggests that the increases in alkaline phosphatase during pregnancy are probably due to increased tension in bile ducts. The results obtained favour the assumption that increased alkaline phosphatase may be due to factors other than the increased metabolism of the bones (*Wetstone et al* 1958) alkaline phosphatase of placental origin (*Kubli* 1961) or steroid action (*McNair* and *Jaynes* 1960) Since the retarded excretion is noted post *partum* compression by the uterus cannot be the cause The results obtained support the view that Oddi's sphincter is subject to spasm during pregnancy (*Westphal* 1923 Gerdes and Boyden 1938)

SUMMARY

A radioactive Rose Bengal test (RB) was performed on 15 women with normal pregnancies and 15 toxaemic patients on the second post-partum day and again 6 weeks later The results obtained were compared with those of other liver function tests carried out simultaneously It was found that the RB test was not so sensitive as bromsulphthalein test (BSP) for indicating hepatic dysfunction during normal pregnancy and toxaemia of late pregnancy The retardation and absence of excretion, seen in the RB excretion curve support the assumption that one of the reasons why alkaline phosphatase increase during pregnancy is the relative obstacle to excretion arising from increased tension of bile ducts

REFERENCES

Antia F P Bharadwaj T P Watsa M C and Master J Lancet II 776 1959

Borglin N E J Clin Endocrinol 19 425 1959

Brewer T H and Hfelte V Am J Obst & Gynec 92 1114 1965

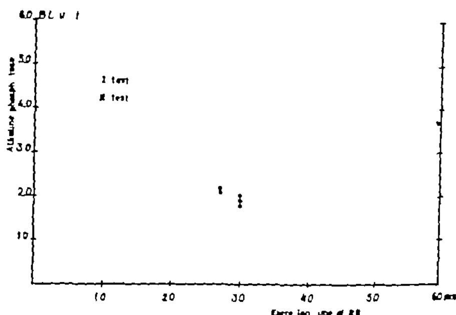


Fig. 4 Comparison of the excretion times of alkaline phosphatase and Rose Bengal.

since the series were so small no far reaching conclusions can be drawn and no comparison of the tests is worthwhile. The low serum proteins of Test I were normalized in 6 weeks a finding that agrees with that of other authors (*Riva*, 1957 *Russell* and *Afonso* 1964) No difference was noted between the toxaemic patients and those with normal pregnancies.

Comparison of the RB and BSP tests reveals, in Test I more increase in the BSP than in the RB values in the toxaemic patients while in the control group the reverse was found. It would seem, therefore that BSP is a more sensitive indicator than the RB test, of the hepatic disorder produced by toxaemia. This may be due to the stress involved in the BSP test. *Brewer* and *Hjelte* (1965) consider BSP a sensitive test for the diagnosis of hepatic dysfunction The large number of contradictory results suggests that RB will not replace BSP in the examination of toxaemic patients. A measurement of radioactivity from blood samples in addition to the external measurement might add to

Pulkkinen, Martti O. and Willman, Kalle. Acta obst. et gynec. scandinav. 46 525, 1967

From the Department of Obstetrics and Gynaecology (Professor L. Rauramo) and the Department of Physiology (Professor K. Hartiala) University of Turku Turku Finland

THE EFFECT OF ORAL CONTRACEPTIVES ON SERUM ENZYMES

BY

MARTTI O. PULKKINEN AND KALLE WILLMAN

There are many reports on the effect of oral contraceptive pills on hepatic function as judged by serum enzyme activity. Eisalo et al. (1964 and 1965) were able to show raised values for aspartate and alanine transaminases. These observations have been confirmed in other publications in Scandinavia (Linthorst, 1964, Palva et al. 1964, and Larsson Cohn, 1966) but have not been found elsewhere (Mears, 1965). Brohult et al. (1965) observed raised serum ornithine carbamoyltransferase activity but in the same women lactate dehydrogenase (LDH) and alkaline phosphatase (AP) activities were normal (Brohult et al. 1965, Bayot, 1966 and Besch et al. 1965). The function of the liver can also be studied by means of other enzyme analyses, including isocitrate dehydrogenase (ICD) and β-glucuronidase (β-G) (King, 1965).

In the investigation reported here the activities of LDH, β-G, ICD and AP were analyzed in the serum of women taking oral contraceptive agents. LDH isoenzymes also were determined. The influences of the menstrual cycle on these enzymes was investigated in a control group of patients. In addition serum AP activity in men was also investigated. These studies were undertaken in order to determine the effects, if any, of different physiological hormonal conditions.

Material and Method

The control group consisted of 30 healthy women between the ages of 22 and 40 years, the average being 27 years. Serum AP

Carelli D Quad. Clin. ostet. ginec. *19* 285 1964
Christhilf S M and *Bonsnes R. W* Am. J. Obst. & Gynec. *59* 1100 1950
Crisp W E. Miesfeld R. L. and *Frajola W J* Obst. & Gynec. *13* 487 1959
Dass A. and *Bhaguanani S* J Obst. & Gynaec. Brit. Cwlth. *71* 727 1964
– J Obstet. Gynaec. India, *14* 655, 1964
Dyrbye M O and *Christensen L. Korsgaard* Acta med. scandinav *167* 239 1960
Friedberg, V Geburtsh. Frauenheilk. *22* 109 1962
Gerdes M M. and *Boyden E A.* Surg. Gynec. & Obst. *66* 145 1938
Haemmerli U P Acta med. scandinav *179* Suppl. *444* 1966
Ingerslev M and *Teilum G* Acta obst. et gynec. scandinav 25 352, 1945
– Ibidem, *31* 74 1945
Kessel M., Ärztl. Lab. *2* 278 1956
Kubli F Gynaecologia *151* 72, 1961
McNair R. D and *Jaynes R. V* Am J Obst. & Gynec. *80* 500 1960
Maqueo M Ayala L C and *Cervantes L.* Obst. & Gynec. *23* 222, 1964
Munnell E. W and *Taylor H C Jr* J Clin. Invest. *26* 952, 1964
Naegeli Th Schweiz. Med. Wschr 59 267 1929
(– Zbl. Chir *56* 1375, 1929)
Nordyke R. A. and *Blahd W H* J.A.M.A. *170* *1159* *1959*
Ojanen R. and *Seppälä O* Ann. Chir et Gyn Fenn. *49* 15 1960
Potter M G J.A.M.A. *106* 1070 1936
Riva G Das Serumeiweissbild, Page 512 Bern, Huber 1957
Russell R. de Alvarez and *Afonso Jose F* Am. J Obst. & Gynec *88* 774 1964
Sherlock S Diseases of the Liver and Biliary System (third edition) 491 1963
Taplin G V Meredith Jr O M Winter C G and *Johnson D* Annals of the New Y Acad Sci *8* 673 1959
Unnérus C E. Ann. Med. Int Fenn *53* *137* *1964*
Westphal K Z. Klin. Med. *96* 95 1923
Wetstone H J Lamotta R. V Middlebrook L Tennant R. and *White B. V* Am J Obst. & Gynec. *76* 480 1958

Received on Nov 11th, 1966

Pulkkinen, Martti O., and Willman, Kalle, Acta obst. et gynec. scandinav. 46, 525 1967

From the Department of Obstetrics and Gynaecology (Professor L. Rauramo) and the Department of Physiology (Professor K. Hartiala) University of Turku Turku Finland

THE EFFECT OF ORAL CONTRACEPTIVES ON SERUM ENZYMES

BY

MARTTI O PULKKINEN AND KALLE WILLMAN

There are many reports on the effect of oral contraceptive pills on hepatic function as judged by serum enzyme activity Eisalo *et al.* (1964 and 1965) were able to show raised values for aspartate and alanine transaminases. These observations have been confirmed in other publications in Scandinavia (Linthorst, 1964 Palva *et al.* 1964, and Larsson Cohn, 1966) but have not been found elsewhere (Mears, 1965) Brohult *et al.* (1965) observed raised serum ornithine carbamoyltransferase activity but in the same women lactate dehydrogenase (LDH) and alkaline phosphatase (AP) activities were normal (Brohult *et al.*, 1965 Bayot, 1966 and Besch *et al.* 1965) The function of the liver can also be studied by means of other enzyme analyses, including isocitrate dehydrogenase (ICD) and β-glucuronidase (β-G) (King, 1965)

In the investigation reported here the activities of LDH, β-G ICD and AP were analyzed in the serum of women taking oral contraceptive agents. LDH isoenzymes also were determined. The influences of the menstrual cycle on these enzymes was investigated in a control group of patients. In addition serum AP activity in men was also investigated. These studies were undertaken in order to determine the effects, if any of different physiological hormonal conditions.

Material and Method

The control group consisted of 30 healthy women between the ages of 22 and 40 years, the average being 27 years. Serum AP
75 50 mU

Cavalli D Quad. Clin ostet. ginec. *19* 285 1964
Christhilf S M and *Bonsnes R W* Am. J Obst. & Gynec. 59 1100 1950
Crisp W E Miesfeld R L and *Frajola W J* Obst. & Gynec. *13* 487 1959
Dass A and *Bhaguwanani S* J Obst. & Gynaec. Brit. Cwlth. *71* 727 1964
– J Obstet. Gynaec India. *14* 655 1964
Dybye M O and *Christensen L Korsgaard* Acta med. scandinav *167* 239 1960
Friedberg, V Geburtsh. Frauenheilk. 22 109 1962
Gerdes M M and *Boyden E A* Surg. Gynec. & Obst. *66* 145 1938
Haemmerli U P Acta med scandinav *179* Suppl. 444 1966
Ingerslev M and *Teilum G* Acta obst. et gynec. scandinav *25* 352, 1945
– Ibidem. *31* 74 1945
Kessel M Ärztl. Lab *2* 278, 1956
Kubli F Gynaecologia *151* 72, 1961
McNal R D and *Jaynes R V.*, Am. J Obst. & Gynec. *80* 500 1960
Maqueo M Ayala L C and *Cervantes L* Obst. & Gynec. *23* 222, 1964
Munnell E W and *Taylor H C Jr* J Clin. Invest *26* 952, 1964
Naegeli Th. Schweiz. Med. Wschr 59 267 1929
(– Zbl Chir *56* 1375 1929)
Nordyke R A and *Blahd W H* J.A.M.A. *170* 1159 1959
Ojanen R and *Seppälä O* Ann. Chir et Gyn. Fenn. *49* 15 1960
Potter M G J.A.M.A. *106* 1070 1936
Riva G Das Serumeiweissbild, Page 512 Bern, Huber 1957
Russell R de Alvarez and *Afonso Jose F* Am. J Obst. & Gynec 83 774 1964
Sherlock S Diseases of the Liver and Biliary System (third edition) 491 1963
Taplin G V Meredith Jr O M Winter C G and *Johnson D* Annals of the New Y Acad Sci. *78* 873 1959
Unnérus C-E Ann. Med. Int Fenn. *53* 137 1964
Westphal K Z. Klin. Med. 96 95 1923
Wetstone H J Lamotta R V Middlebrook L Tennant R and *White B V* Am. J Obst & Gynec. *76* 480 1958

Received on Nov 11th, 1966

Table III. *The Effect of Various Oral Contraceptive Agents on Serum ICD and AP Activities*

	ICD					AP				
	M	S E		p		M	S E.		p	
Anovlar	7 7	1.2	9	<0 1	14	4 9	5	16	<0.001	7
Ortho-Novin	6 5				7	3 1		1		1
Conovid-E						8.1				26
Lyndiol 2 5	10.	2.1	7	<0.00	6	8.	2.2	3		3
Sequential pill	1 9	4 5	6	<0.02		8 6				
Volidan (balanced)	2				2	4 3	1.1	2	<0 001	
Progestagenic pills	8 6	1.4	0	< 0	5	4 8	5	17	<0.00	7
Oestrogenic pills	9	3	3	<0.0	5	8.2		5		3

M=mean value S E = standard error of the mean, n=number of determinations, p=significance of difference =the mean number of cycles when using pills.

was determined in 30 healthy men from 20 to 45 years of age. 75 women taking oral contraceptives were studied and in most cases several determinations were made Their ages varied from 19 to 38 years, the mean age being 26 years. The analyses undertaken are shown in Tables I–III. The following oral contraceptive pills were used Lyndiol 2 5[R] (lynestrenol 2.5 mg + mestranol 0 075 mg) Anovlar[R] (norethisterone acetate 4 mg + ethinylestradiol 0.05 mg) Volidan[R] (megestrol acetate 4 mg + ethinylestradiol 0.05 mg) Ortho-Novin[R] (norethisterone 2 mg + mestranol 0.1 mg) Conovid-E[R] (norethynodrel 2.5 mg + mestranol 0.1 mg) One group of women had a sequential regime (Organon) taking 0.08 mg mestranol for the first 15 days and then Lyndiol 2.5 for the subsequent 7 days. In this group blood samples were taken from 11th to 15th days after the first dose of mestranol. From women taking the other pills, the samples were taken at random times during the cycle

The oral contraceptives used were grouped into three categories (Mears, 1965) These groups are detailed in Tables I IV The first is clinically the most oestrogenic group, and includes Lyndiol 2 5, Conovid-E and the sequential pills. Anovlar

Table I. Serum Enzyme Activities in a Control Group and Group of Women Taking Oral Contraceptives

Analysis	Normal Group			Treated Group				
	M	S.E.		M	S.E.		p	
LDH total	103	4.6	17	82	3.4	32	<0.01	7
fraction I	25.1	1.5	14	24.8	1.2	18		6
II	42.7	1.4	14	43.6	2.5	18		6
III	26.8	1.4	14	25.5	2.0	18		6
IV	5.5	1.0	14	5.8	0.9	18		6
β-G	129	7.8	19	253	14.5	37	<0.001	7
ICD	3.4	0.4	13	9.6	1.4	24	<0.01	8
AP	8.4	0.6	25	5.4	0.5	24	<0.001	6

M=mean value S.E.=standard error of the mean, n=number of determinations p=significance of difference c=the mean number of cycles when using pills.

Table II. *The Effect of Various Oral Contraceptive Agents on Serum LDH and β-G Activities*

	LDH					β-G			
	M	S.E.		p		M	S.E.		p
Anovlar	78	3.9	19	<0.001	7	303	27.1	12	<0.001
Ortho-Novin	57		1		11	123	8.5	2	
Conovid E	81		1		28				
Lyndiol 2.5	95	10.8	6		4	212	18.7	10	<0.001
Sequential pill	105	1.0	2		2	281	22.7	10	<0.001
Volidan (balanced)	78	2.4	3	<0.001	3	182	12.1	3	<0.01
Progestagenic pills	77	3.8	20	<0.001	7	278	28.9	14	<0.001
Oestrogenic pills	85	7.3	9		4	247	16.3	20	<0.001

M=mean value S.E.=standard error of the mean, n=number of determination p=significance of difference c=the mean number of cycles when using pills.

Table III. *The Effect of Various Oral Contraceptive Agents on Serum ICD and AP Activities*

	ICD					AP				
	M	S.E.		P		M	S.E.		P	
Anovlar	7 7	1.2	9	< 0	14	4 9	5	16	< .00	7
Ortho-Novin	6 5				17	5.1				11
Conovid-E						6.1				16
Lyndiol 5	10 1	2.	7	< .001	6	8.1	2.2	3		3
Sequential pill	1.9	4 5	6	<0 02		8 6				
Volidan (balanced)	2				2	4 3	.1		<0,001	
Progestagenic pills	8 6	.4	1	<0.01	5	4 8	0 5	17	<0 00	7
Oestrogenic pills	1 9	3 3	3	<0 01	5	8	1	5		3

M=mean value, S.E.=standard error of the mean, n=number of determinations p=significance of difference, c=the mean number of cycles when using pills.

was determined in 30 healthy men from 20 to 45 years of age. 75 women taking oral contraceptives were studied and in most cases several determinations were made. Their ages varied from 19 to 38 years the mean age being 26 years. The analyses undertaken are shown in Tables I–III. The following oral contraceptive pills were used Lyndiol 2 5[R] (lynestrenol 2.5 mg + mestranol 0.075 mg) Anovlar[R] (norethisterone acetate 4 mg + ethinylestradiol 0.05 mg) Volidan[R] (megestrol acetate 4 mg + ethinylestradiol 0.05 mg) Ortho-Novin[R] (norethisterone 2 mg + mestranol 0.1 mg) Conovid-E[R] (norethynodrel 2.5 mg + mestranol 0 1 mg) One group of women had a sequential regime (Organon) taking 0.08 mg mestranol for the first 15 days and then Lyndiol 2 5 for the subsequent 7 days. In this group blood samples were taken from 11th to 5th days after the first dose of mestranol. From women taking the other pills, the samples were taken at random times during the cycle

The oral contraceptives used were grouped into three categories (Mears, 1965) These groups are detailed in Tables I IV The first is clinically the most oestrogenic group and includes Lyndiol 2.5, Conovid-E and the sequential pills. Anovlar

Table I. *Serum Enzyme Activities in a Control Group and Group of Women Taking Oral Contraceptives*

Analysis	Normal Group			Treated Group				
	M	S.E.		M	S.E.		p	c
LDH total	103	4.6	17	82	3.4	32	<0.01	7
fraction I	25.1	1.5	14	24.8	1.2	18		6
II	42.7	1.4	14	43.6	2.5	18		6
III	26.8	1.4	14	25.5	2.0	18		6
IV	5.5	1.0	14	5.8	0.9	18		6
β-G	179	7.8	19	253	14.5	37	<0.001	7
ICD	3.4	0.4	13	6.6	1.4	4	<0.01	8
AP	8.4	0.6	25	5.4	0.5	24	<0.001	6

M=mean value, S.E.=standard error of the mean, n=number of determinations p=significane of difference c=the mean number of cycles when using pills.

Table II. *The Effect of Various Oral Contraceptive Agents on Serum LDH and β-G Activities*

	LDH					β-G				
	M	S.E.		p		M	S.E.		p	
Anovlar	78	3.9	19	<0.001	7	303	27.1	12	<0.001	14
Ortho-Novin	57		1		11	123	8.5	2		12
Conovid E	81		1		28					
Lyndiol 2.5	95	10.8	6		4	212	18.7	10	<0.001	6
Sequential pill	105	1.0	2		2	281	22.7	10	<0.001	2
Volidan (balanced)	78	2.4	3	<0.001	3	182	12.1	3	<0.01	2
Progestagenic pills	77	3.8	20	<0.001	7	278	28.9	14	<0.001	13
Oestrogenic pills	95	7.3	9		4	247	16.3	20	<0.001	4

M=mean value S.E.=standard error of the mean, n=number of determinations, p=significance of difference c=the mean number of cycles when using pills.

was determined according to Fishman *et al.* (1962) but using a glycine-sodium hydroxide buffer pH = 9.0 which was 0.1 m in Mg. β-Glycerophosphate in a final concentration of 0.06 M was used as substrate.

β-G activity was determined by the method of Fluke (196). Disc electrophoresis on polyacrylamide gel (Davis *et al.*, 1964) was used to separate the LDH isoenzymes. Isoenzyme bands were made visible by incubating the gels at +37 C in a solution (5.0 ml per gel) which was made up of 3 ml of 0.1 M Tris-HCl buffer 5 ml of nitro blue tetrazolium solution (5 mg/1 ml of distilled water) 0.5 ml of phenazine methosulphate solution (5 mg/ ml distilled water). The reaction was stopped by inserting the gels into 5 per cent acetic acid. The activity of the individual isoenzymes was determined by measuring the colour intensity of the bands with microdensitometer (Joyce & Loebl) connected to a recorder. The activities of the isoenzyme fractions were estimated by weighing the peaks cut from the diagram.

Serum alanine transaminase activity (SGPT) was measured with a commercial kit (Boehringer Farb-Test) as a clinical routine test. 69 women were studied, of whom 31 used Anovlar 1 Conovid-E, 5 Lyndiol 5, 3 Ortho-Novum, 7 Volidan, and 12 mestranol. The normal limits for SGPT with the method used are 0.5–9.0 m-I.U. mean 3.7 m-I.U.

All the determinations were made in duplicate. The activities of LDH, ICD AP and SGPT are expressed in milli International Units (m-I.U.) and that of β-G in micro International Units (μ-I.U.). LDH isoenzymes are expressed as percentages of the total activity.

Results

Serum enzyme activities in normal women and in women taking oral contraceptives are shown in Table I. The significance of the results is also shown. It can be seen that women taking oral contraceptives have a higher β-G and ICD level and lower LDH and AP level in serum compared to the control group. There are no significant changes in LDH isoenzymes.

The effect of various oral contraceptives on serum LDH and β-G activities is shown in Table II. Oestrogenic pills have no effect on LDH but the progestagenic pills lower the activity. Of the individual preparations Anovlar depresses the LDH activity

The authors are indebted to the Laboratory of the Central Hospital of Turku for these analyses.

The authors are indebted to H. Uppönen, B. Sc. for the statistical analysis of the data by computer.

and Ortho-Novin were considered to be the most progestagenic pills Volidan represents an intermediate formulation.

Two male and two female volunteers took Anovlar for seven days. Blood samples were collected every morning and afternoon before and during this period.

With this exception all the blood samples were collected in the morning to minimize the effect of diurnal variations All the samples were taken from the cubital vein straight into a centrifuge tube in which the blood was allowed to clot. Thereafter the sample was centrifuged immediately The sera obtained in this way were then kept at +4 C All determinations were made on the same day o to 2 normal sera were analyzed each day during the study Samples showing the slightest haemolysis were discarded. The analyses were performed by the same laboratory technician using the same methods throughout the period of investigation.

In the LDH determination the final reaction mixture (1 0 ml) was 0 05 M in phosphate buffer 0.05 M in sodium d,l lactate and 0.001 M in nicotinamide adenine dinucleotide (NAD) Serum was pipetted 10 μl. The final pH was 7 5. The reaction was followed in a Perkin Elmer double beam spectrophotometer with a temperature controlled cell holder an ordinate scale expansion accessory and an external recorder The change in absorption at 340 mμ was followed for about seven minutes using a 14-fold expansion and paper speed of 24 inches/hour Activity was calculated by drawing a tangent at the origin of the curve.

ICD activity was determined as follows into a test tube was pipetted 0 3 ml of buffer (a 0 1 M tris-(hydroxymethyl) aminomethane (Tris) HCl buffer ph=9.0 which was 0.004 M in Mg and 0.002 M in dipotassium ethylenediaminetetra-acetate) 0 1 ml of serum and 0 1 ml of 0.0015 M nicotinamide adenine dinucleotidephosphate.

The mixture was then incubated for 10 minutes in a +37 C water bath and 0.05 ml of 0.1 M trisodium d,l-isocitrate solution was added. Four such tubes were prepared. After five minutes two of the tubes were removed from the water bath and 2.0 ml of 0.01 M sodium hydroxide solution was pipetted into them. In the two tubes left the reaction was stopped in the same way after 25 minutes. The quantity of the reduced coenzyme which appeared during 20 minutes of the reaction time was measured in an Aminco Bowman spectrophotofluorometer using an excitation wave length of 340 mμ and emission at 457 mμ (Udenfriend 1962) The quantity of the reduced coenzyme was calculated from a standard curve. In preliminary experiments the reaction was found to be linear for at least 35 minutes and the so-called lag period did not exceed three minutes in these conditions. AP

was determined according to Fishman et al. (1960) but using a glycine-sodium hydroxide buffer ph=9.0 which was 0.01 m in Mg. β-Glycerophosphate in a final concentration of 0 6 M was used as substrate.

β-G activity was determined by the method of Plaice (1961). Disc electrophoresis on polyacrylamide gel (Davis et al., 1964) was used to separate the LDH isoenzymes. Isoenzyme bands were made visible by incubating the gels at +37 C in solution (5.0 ml per gel) which was made up of 3.0 ml of 1 M Tris-HCl buffer 5 ml of nitro blue tetrazolium solution (5 mg/1 ml of distilled water) 5 ml of phenazine methosulphate solution (0.5 mg/1 ml distilled water). The reaction was stopped by inserting the gels into 5 per cent acetic acid. The activity of the individual isoenzymes was determined by measuring the colour intensity of the bands with a microdensitometer (Joyce & Loebl) connected to a recorder. The activities of the isoenzyme fractions were estimated by weighing the peaks cut from the diagram.

Serum alanine transaminase activity (SGPT) was measured with commercial kit (Boehringer Farb-Test) as a clinical routine test. 69 women were studied, of whom 3 used Anovlar 1 Conovid-E, 5 Lyndiol 2.5, 3 Ortho-Novum, 7 Volidan, and 12 mestranol. The normal limits for SGPT with the method used are 0.5-9 m-I.U. mean 3.7 m-I.U.

All the determinations were made in duplicate. The activities of LDH, ICD AP and SGPT are expressed as milli International Units (m-I.U.) and that of β-G in micro International Units (μ-I.U.). LDH isoenzymes are expressed as percentages of the total activity.

Results

Serum enzyme activities in normal women and in women taking oral contraceptives are shown in Table I. The significance of the results is also shown. It can be seen that women taking oral contraceptives have a higher β-G and ICD level and lower LDH and AP level in serum compared to the control group. There are no significant changes in LDH isoenzymes.

The effect of various oral contraceptives on serum LDH and β-G activities is shown in Table II. Oestrogenic pills have no effect on LDH, but the progestagenic pills lower the activity. Of the individual preparations Anovlar depresses the LDH activity

The authors are indebted to the Laboratory of the Central Hospital of Turk for these analyses.

The authors are indebted to H. Löppönen, B. Sc. for the statistical analysis of the data by computer.

but the effect of Lyndiol 2 5 is not statistically significant. The difference between the effect of Lyndiol 2 5 and Anovlar is not significant ($p < 0 \cdot 1$) No specific effects on the LDH isoenzymes could be demonstrated. As far as β-G activity is concerned, it can be seen that Lyndiol 2 5, Anovlar and the sequential regime cause an increase in activity Among these Anovlar has a greater potency as compared with Lyndiol 2 5 ($p < 0.05$)

The effect of the different pills on serum ICD and AP activities is demonstrated in Table III. ICD activity is increased with all preparations for which enough statistical evidence is available. There is no significant difference among the various pills. AP activity is not affected by the oestrogenic group of pills but is decreased by the other preparations. The difference between the groups is significant ($p < 0 \cdot 02$)

Mean SGPT activity was within normal limits in all the groups. Values above the upper normal limit were encountered with various pills as follows Anovlar 3 Volidan 1 and sequential pill 1 *All these values were below 13 m I U*

The effect of the menstrual cycle on the analyzed parameters in the normal group was examined by means of analysis of variance. No correlation was found. Also the duration of administration of oral contraceptives was without demonstrable effect

In Figures 1–4 the effect of Anovlar on serum LDH, β-G ICD and AP in the 4 volunteers is shown. The first two columns represent the men and the third and fourth the women who took part in the experiment. Each column shows the mean value of the morning and afternoon samples. On the second morning they began to take Anovlar and this was continued for seven days. The changes are similar to those found in women taking oral contraceptives, except with regard to ICD The changes became noticeable about the third day after the first pill. In preliminary experiments similar results were obtained with a single pill.

It was found in preliminary studies that serum AP isoenzymes in nine treated women did not show any tendency to differ from those of a normal group

AP activity in 30 healthy men was 14 8 ± 0 8 m I.U There is

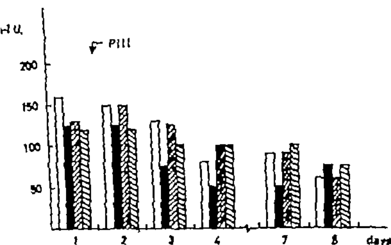


Fig. The changes taking place in LDH activity during Anovlar administration. (for details see text)

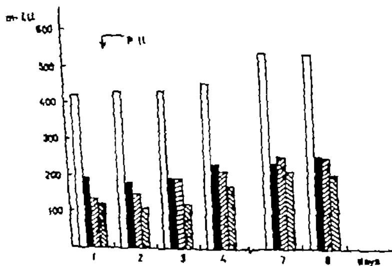


Fig. 2. The changes taking place in β-G activity during Anovlar administration. (for details see text)

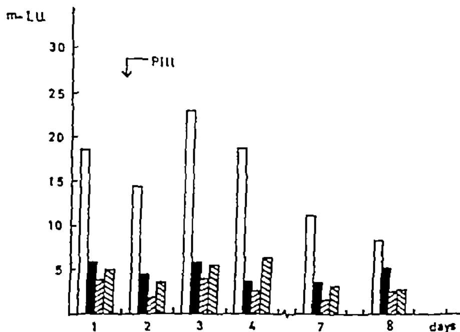


Fig. 3 The changes taking place in ICD activity during Anovlar administration. (for details see text)

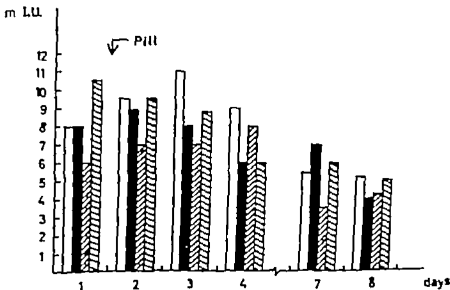


Fig. 4. The changes taking place in AP activity during Anovlar administration. (for details see text)

a significant difference between AP activity in normal men and in normal women ($p < 0.001$)

Discussion

It has been claimed that the function of steroid hormones in an organism would depend on their regulatory effect on enzymatic reactions. In tissues, many enzymes have been found to be under hormonal control. Less is known about the relationship between hormones and enzymes in serum. Also, the physiology of serum enzymes is for the most part unknown (Hess, 1962) Serum enzyme analyses are mostly used in some pathological conditions in which damaged tissues provide the serum with new enzymes or effect the activities of pre-existing ones It is therefore supposed that the changes taking place in the activity of serum enzymes can be brought about in two different ways.

It has been shown earlier that neither the sex nor the stage in the menstrual cycle (Donayre *et al.* 1965) (King, 1965) have any effect on serum LDH activity Raised values have been encounted in the serum of pregnant women, in the foetal umbilical cord (Pulkkinen *et al.* 1966) and in childhood (Hill, 1956) It was possible through this work to confirm the earlier observations that the menstrual cycle does not affect LDH activity In disorders of the liver serum LDH activity is normal or slightly elevated (Hess, 1962) Earlier it was not possible to show any effect of oral contraceptive pills on serum LDH (Bayot, 1966) The slight decrease in activity found in this investigation may be regarded as hormonal in origin because the effect could be found in both the sexes without any changes in food intake habits or muscular activity Because the isoenzyme pattern remained the same, it is possible that the changes are not confined to a single organ. One possibility is that elimination from the serum is accelerated.

Oestrogens raise the activity of β-G in the liver (Fishman, 1961) and in serum (Kasdon *et al.*, 1960) All the compounds taken increased the activity (with the exception of Ortho-Novin taken by two women) with no significant differences between them. The changes of activity in serum may reflect elevated β-G

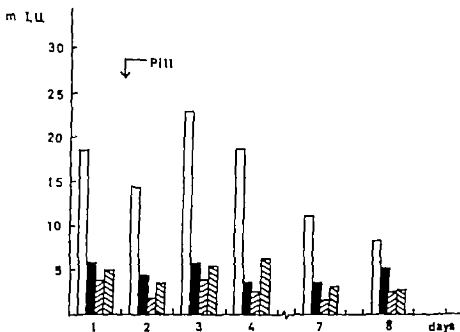


Fig. 3 The changes taking place in ICD activity during Anovlar administration. (for details see text)

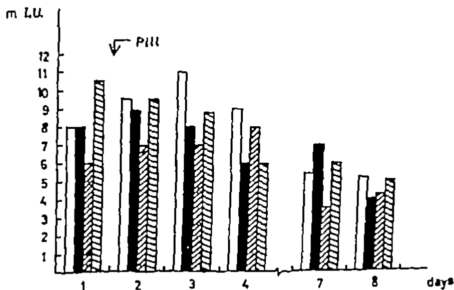


Fig. 4. The changes taking place in AP activity during Anovlar administration. (for details see text)

deleterious to the organism. When using clinical enzyme analyses with women taking oral contraceptives, new normal values must be taken as a starting point.

SUMMARY

Serum lactate dehydrogenase, β-glucuronidase, alkaline phosphatase isocitrate dehydrogenase, lactate dehydrogenase isoenzymes and alanine transaminase were studied in normal women and in women taking oral contraceptives. Alkaline phosphatase was also determined in normal men. Men had higher alkaline phosphatase activity in serum as compared with women. Oral contraceptive decreased serum lactate dehydrogenase and alkaline phosphatase but elevated β-glucuronidase and isocitrate dehydrogenase activity Various preparations had different influences on these parameters. They had no effect on lactate dehydrogenase isoenzymes. Mean alanine transaminase activity was within normal limits. The changes, except in isocitrate dehydrogenase activity became visible during the first three days after the first pill had been taken. They were parallel in both the sexes. It has been suggested that the results of this investigation could be taken into account in clinical enzyme diagnostic studies.

REFERENCES

Antonioli J A Baer A and Vannotti A Acta Haemat 34 29, 965
Bayor D Research on Steroids 2 533, 966
Beach P K Vorys N Ullery J C, Stevens V and Barry R D Metabolism 14, 987 965
Brohult J and Westgren A Lancet 2 344 965
Berger H L and Leonhardt K, Arch. Gynäk. 81 300, 1952
Clark L C and Beck, E J J. Pediat. 36, 335 950
Davis B J and Ornstein L, Ann N Y Acad Sc 2 404, 964
Demeyre J and Pincus Gr J. Clin Endocrinol Metab 5, 432 965
Eisalo A Heinonen P A and Luukkainen T Brit. M. J. 2 426 964
Brit M J 4 8, 965
Fishman, W H Chemistry of Drug Metabolism, C C Thomas, Springfield, 27 96
Fishman W H Green S and Inglis N I, Biochim Biophys. Acta 6 363, 962

activity in the liver The menstrual cycle had no effect on the activity This finding is in accordance with previous reports (King, 1965)

Raised values of serum ICD activity are encounted only in hepatic dysfunction (Sterkel *et al*, 1958) In this investigation the doubling of the mean value in ICD activity in women taking pills could originate in the liver but some other mechanism may be involved. Raised ICD values are met also in normal pregnancy (Pulkkinen *et al*, 1966)

The serum activity of AP may be under hormonal control because it was possible to show in this work that normal men showed a greater activity than normal women. Women taking contraceptive agents showed the lowest level of activity The difference in activity in the sexes has been noted earlier (Clark *et al*, 1950) It has been reported that oestrogens have a stimulatory effect on leucocyte phagocytic activity (Burger *et al* 1952) On the other hand it is known that a combination of an oestrogen and progestagen but not oestrogen alone increases the AP activity in leucocytes (Antoniolli *et al*. 1965) Goldstein (1965) observed that an oral contraceptive pill had a similar effect. Thus the diminution of AP activity in serum would only represent an increased capture of enzyme molecules by leucocytes Another possible mechanism depends on the ability of contraceptive agents to increase serum corticoid concentration (Sala *et al* 1966) which in turn increases AP activity in leucocytes (Valentine *et al* 1957) In hepatic dysfunction AP activity in serum is raised (King, 1965) Some haematological disorders are associated with lowered values (King, 1965) Parallel changes then can be found in leucocytes (McCoy *et al* 1965) It is therefore possible that a certain balance is maintained between serum and leucocyte AP which could be affected by oral contraceptives.

As far as the oestrogenic and progestagenic pills are concerned it can be said that neither group cause more disturbances than the other in the parameters studied. Because the normal liberation of serum enzymes from tissues and their turn-over and elimination are for the most part unknown it is not possible to predict the way in which these changes caused by pills may be

deleterious to the organism. When using clinical enzyme analyses with women taking oral contraceptives new normal values must be taken as a starting point.

SUMMARY

Serum lactate dehydrogenase, β-glucuronidase, alkaline phosphatase, isocitrate dehydrogenase, lactate dehydrogenase isoenzymes and alanine transaminase were studied in normal women and in women taking oral contraceptives. Alkaline phosphatase was also determined in normal men. Men had higher alkaline phosphatase activity in serum as compared with women. Oral contraceptive decreased serum lactate dehydrogenase and alkaline phosphatase but elevated β-glucuronidase and isocitrate dehydrogenase activity Various preparations had different influences on these parameters. They had no effect on lactate dehydrogenase isoenzymes. Mean alanine transaminase activity was within normal limits. The changes, except in isocitrate dehydrogenase activity became visible during the first three days after the first pill had been taken. They were parallel in both the sexes. It has been suggested that the results of this investigation could be taken into account in clinical enzyme diagnostic studies.

REFERENCES

Aurondoth, I A Baer A and *Vannotti A*., Acta Haemat 34, 29 965
Bayon D Research on Steroids 313, 966
Beach, *P K Vorys, N Ullery I C Stevens V* and *Barry R.* D Metabolism 14 387 963
Brohult J and *Westgren A* Lancet 344 965
Berger H and *Leonhardt K*. Arch. Gynäk. 8 300 952
Clark *L C* and *Beck E J* J Pediat 36 335, 950
Davis B J and *Ornstein, L* Ann. N Y Acad Sc 2 404, 1964
Doucette J and *Pincus, G* J. Clin. Endocrinol Metab 3, 432, 965
Eisalo A Järvinen P A. and *Luukkainen T* Brit. M. J. 426 1964
Brit. M. J 14 6, 963
Fishman W H Chemistry of Drug Metabolism, C C Thomas, Springfield, 37 961
Fishman, W H Green S and *I glu N I* Biochem. Biophys. Acta 62 363, 98

Goldstein D P Obst. and Gynec. 25 413, 1965
Hess B Enzyme im Blutplasma G Thieme Stuttgart, 1962
Hill B. R. Cancer Res. 16 460, 1956
Kasdon S C. Romano P and *Hatzimichael A.*, Obst. and Gynec. 15, 367 1960
King, J Practical Clinical Enzymology Van Nostrand, London, 241 1965
Larsson-Cohn U., Acta obst. et gynec. scandinav 45 196 1966
Linthorst G. Brit. M. J. 2 920, 1964
McCoy E. E. Park J and *England J.*, Clin. Chem. Acta 12 453, 1965
Mears E. Handbook on oral contraception, Churchill, London, 1965
Palva I P Mustala O. O Brit. M. J 2 688, 1964
Plaice C. *H J* Clin. Path. 14 661 1961
Pulkkinen M. and *Willman K.* Acta Physiol. Scand. 68 suppl. 277 167 1966
– Unpublished observations
Sala G and *Castegnaro E.* Research on Steroids 2, 405, 1966
Sterkel, R. L., Spencer J A. Wolfson S R. Jr and *Williams Ashman H. G* J Lab. Clin. Med. 52 176, 1958
Stoll, B. A., Andrews J T and *Motterman R.*, Brit. M. J 1 960 1966
Udenfriend S. Molecular Biology N Y Acad. Press, New York, 247 1962
Valentine W N Follette J H Salomon D H and *Reynolds J* J. Lab. clin. Med. 49, 723, 1957

Received on Jan. 7th, 1967

Nilsson, A., Jacobson, L., and Ingemanson, C.-A. Acta obst. et gynec. scandinav. 46, 537 1967

From the Department of Psychiatry I (Prof. Erik Essen-Möller) and the Department of Obstetrics and Gynaecology (Prof. Alf Sjövall) University of Lund, Sweden

SIDE EFFECTS OF AN ORAL CONTRACEPTIVE WITH PARTICULAR ATTENTION TO MENTAL SYMPTOMS AND SEXUAL ADAPTATION

BY

A. NILSSON, L. JACOBSON, AND C.-A. INGEMANSON

The increasing use of oral contraceptives in recent years has been accompanied by an increased knowledge of effects and side-effects of a somatic, especially gynaecological, and biochemical nature which such medication can bring about. So far however very little attention has been paid to effects and side-effects of psychiatric and psychological nature. Only a very few studies have focused on or dealt with these problems. Most studies have been carried out on private patients and on small samples, which may imply a bias or at least a selection. The results are controversial: in some studies (*Hauser* and *Schubiger* 1965, *Kaye* 1963, *La Gravinese* 1965) a relation between oral contraceptive administration and the occurrence of psychoneurosis or depression has been suspected, in others (*Zell* and *Crisp* 1964, *Bakker* and *Dightman* 1966, *Linthorst* 1966) no such relationship was found. The latest extensive report of the American Food and Drug Administration, 1966 (FDA, 1966) states that at present no precise data are available on this point.

The motive for starting the present investigation was the clinical impression that there may sometimes exist a relation between oral contraceptive administration and the appearance of neurotic symptoms. The investigation was designed as a retrospective study and the results must be judged cautiously with regard to many bias factors, which will be thoroughly discussed.

Material and method

The sample comprises all women who were prescribed an oral contraceptive during 1964 at the Department of Obstetrics and Gynaecology Lund. No selection has been made it includes all women who received the drug during the year not only for contraceptive purpose but also as gynaecological therapy

In March, 1966, the women received a comprehensive questionnaire in which the main emphasis was placed upon a survey of possible emotional changes in connection with the use of the ovulation inhibitor Questions were also included about previous psychiatric problems or insufficiencies

The questionnaire also included a scale for the measurement of personality characteristics according to Sjobring s personality theory (*Sjöbring*, 1958) The scale, the MNT-scale (*Nyman* and *Marke* 1961) includes the dimensions validity (degree of possible energetic investment) stability (degree of emotional control) and solidity (degree of long range organization) For a more complete description see *Nyman* 1956 *Nyman* and *Marke* *1961 Andersson, 1962 Marke, 1963 The scale consists of three* homogenous and fairly orthogonal scales measuring the above mentioned dimensions each including 20 items. The dimensions are assumed to vary continuously according to the normal distribution and to be independent of each other (*Nyman* and *Marke* 1961) The subjects were divided by median cuts into two groups for each one of the three variables of validity stability and solidity of the MNT scale The group above the median constituted the supervariant of the dimension and the group *below the median the subvariant*

Questions about the occurrence of a number of somatic and gynaecological changes were also taken up A survey of such factors in addition to its intrinsic interest is also of importance for a wider evaluation of the purely psychiatric variables and correlations The inclusion of somatic and gynaecological questions was also *considered advisable in order to reduce* the bias which could arise with a questionnaire of a purely psychiatric nature.

Anovlar® Schering AG Berlin. Norethisterone acetate 4 mg, Ethinyloestradiol 0.05 mg.

Table I. *The Sample*

Number of women prescribed Anovlar® in 1964 (Questionnaires sent)	344
Subjects not found by post	6
Unanswered questionnaires	25
Answers received	313 (91.0 %)
Number of women who used tablets for less than 1 month or not at all	32
Final sample	281

In order to avoid giving the impression that the survey only concerned negative side-effects, the questions were formulated so as to register changes in both a positive and a negative direction. In questions concerning the effects of the tablets the women were always asked to make comparisons with their condition *during the year before* the treatment began. The majority of the questions required simple alternative answers yes or no, some included a number of fixed alternatives, and only a few were of the open question type.

A number of background variables were obtained from the hospital records

344 women had Anovlar® prescribed in 1964 and thus comprised our series. The losses are shown in Table I the final sample comprises 281 subjects. The internal loss—that is unanswered items—was very low

Table II shows the distribution of subjects according to age parity social status and marital state. The drug was prescribed for contraception only to 259 of the women. The remaining 22 women had the tablets prescribed because of endometriosis. The latter group will be dealt with separately because they were regarded as a loaded group.

Results

In order to avoid or *diminish* the influence of the wording of the specific questions, the subjects were first requested to state how

Material and method

The sample comprises all women who were prescribed an oral contraceptive during 1964 at the Department of Obstetrics and Gynaecology Lund. No selection has been made it includes all women who received the drug during the year not only for contraceptive purpose but also as gynaecological therapy

In March, 1966, the women received a comprehensive questionnaire in which the main emphasis was placed upon a survey of possible emotional changes in connection with the use of the ovulation inhibitor Questions were also included about previous psychiatric problems or insufficiencies.

The questionnaire also included a scale for the measurement of personality characteristics according to Sjöbring's personality theory (*Sjöbring*, 1958) The scale the MNT-scale (*Nyman* and *Marke* 1961) includes the dimensions validity (degree of possible energetic investment) stability (degree of emotional control) and solidity (degree of long range organization) For a more complete description see *Nyman* 1956 *Nyman* and *Marke* 1961 *Andersson* 1962 *Marke* 1963 The scale consists of three homogenous and fairly orthogonal scales measuring the above mentioned dimensions each including 20 items. The dimensions are assumed to vary continuously according to the normal distribution and to be independent of each other (*Nyman* and *Marke* 1961) The subjects were divided by median cuts into two groups for each one of the three variables of validity stability and solidity of the MNT-scale The group above the median constituted the supervariant of the dimension and the group below the median the subvariant

Questions about the occurrence of a number of somatic and gynaecological changes were also taken up. A survey of such factors in addition to its intrinsic interest, is also of importance for a wider evaluation of the purely psychiatric variables and correlations. The inclusion of somatic and gynaecological questions was also considered advisable in order to reduce the bias which could arise with a questionnaire of a purely psychiatric nature.

Anovlar® Schering AG Berlin. Norethisterone acetate 4 mg, Ethinyloestradiol 0.05 mg.

Table III. *Duration of Use of the Oral Contraceptive*

Months	No.	%
1–3	23	8.9
4–6	35	13.5
7 12	52	20.1
>12	144	55.6
Unanswered	5	1.9
Total	259	100

Table IV *Causes of Cessation*

Stated cause of cessation	No	%	% of total material
Side-effects	91	65.9	35.1
Fear of side-effects	11	8.0	4.3
Desire for pregnancy or pregnancy due to careless use of medication	19	13.8	7.3
Other reasons	13	9.4	5.0
Unanswered	4	2.9	1.5
Total	138	100	

most frequently reported, 26.1 and 23.9 per cent respectively. Side-effects of a somatic nature, nausea and weight gain excluded, were less frequently reported, 14.9 per cent.

To assess changes of weight, the women were asked to report their usual weight the year before they started with the tablets as well as their weight at the time of investigation. Subjects having discontinued before this time were requested to state their weight at cessation. 40.9 per cent reported a weight gain within 2.5 kg, 15.8 per cent a weight increase of more than 5 kg, while 8.9 per cent reported a weight decrease (Table VI).

Dysmenorrhoea before the start of the oral contraceptive administration was reported as slight to moderate in 57.5 per cent and severe in 12.7 per cent of cases. During the use of Anovlar® the complaints were reduced to 20.8 and 1.2 per cent

Table II. *Age Parity Social Group and Marital State*

Age in years	20	20–24	25–29	30–34	35–39	>39
Contraception	7	43	63	73	53	20
Endometriosis	0	2	3	6	3	8

Parity	0	1	2	3	4	5	>5
Contraception	20	44	86	67	28	13	1
Endometriosis	11	6	3	2	0	0	0

Social group	I	II	III
Contraception	78	75	106
Endometriosis	5	10	7

Marital state	married	unmarried	divorced	widowed
Contraception	239	16	4	0
Endometriosis	19	2	0	1

long they had been using the oral contraceptive and, in case of cessation or temporary interruption, to state the cause. 121 women (46 7 per cent) were still using the tablets at the time of investigation, while 138 (53 3 per cent) had discontinued, 91 (35 1 per cent) due to various side-effects. The duration of use of the contraceptive is shown in Table III Women having used the tablets for less than 12 months are not always the same as those discontinuing, because some had temporary interruptions due to pregnancy or other causes

In Table IV the reasons for definite cessation are shown. For those cases reporting *side-effects* as the cause of cessation, a detailed account is given in Table V Some subjects reported more than one symptom, and the frequencies given include all of them. It should be borne in mind that the frequency figures here only refer to symptoms which were *the cause of cessation* As can be seen weight gain and mental disturbances were the

Table III. *Duration of Use of the Oral Contraceptive*

Months	No.	%
1 3	23	8.9
4–6	35	13.5
7–12	52	20.1
>12	144	55 6
Unanswered	5	1.9
Total	259	100

Table IV *Causes of Cessation*

Stated cause of cessation	No	%	% of total material
Side-effects	91	65 9	35.1
Fear of side-effects	11	8 0	4 3
Desire for pregnancy or pregnancy due to careless use of medication	19	13 8	7.3
Other reasons	13	9 4	5 0
Unanswered	4	2.9	1 5
Total	138	100	

most frequently reported, 26.1 and 23.9 per cent respectively Side-effects of a somatic nature, nausea and weight gain excluded, were less frequently reported, 14.9 per cent.

To assess changes of weight, the women were asked to report their usual weight the year before they started with the tablets as well as their weight at the time of investigation. Subjects having discontinued before this time, were requested to state their weight at cessation. 40.9 per cent reported a weight gain within 2 5 kg, 15.8 per cent a weight increase of more than 5 kg, while 8.9 per cent reported a weight decrease (Table VI)

Dysmenorrhoea before the start of the oral contraceptive administration was reported as slight to moderate in 57.5 per cent and severe in 12.7 per cent of cases. During the use of Anovlar® the complaints were reduced to 20.8 and 1.2 per cent as seen

Table V *Side Effects Stated to be the Cause of Cessation (91 Subjects)*

Side-effects	%	
Psychiatric symptoms	23.9	43.3
Tiredness	9 7	
Decrease of libido	9 7	
Weight gain	26 1	
Nausea	15.7	
Somatic symptoms	14.9	

Table VI. *Weight Changes During Anovlar® Administration in Relation to Average Weight During the Year Before Use*

Weight change	No.	%
Decrease >5 kg	5	1.9
Decrease 2-5 kg	18	7 0
Unchanged within + - 2 kg	79	30.5
Increase 2-5 kg	106	40.9
Increase >5 kg	41	15.8
Data not available	10	3.9
Total	259	

respectively The frequency of occurrence of a heavy menstrual flow was reduced during administration from 33.5 to 4 2 per cent.

The questionnaire included three items regarding premenstrual tension namely feeling of distendedness irritability and feeling of depression prior to menstruation. 70 9 per cent of the subjects who had experienced premenstrual tension symptoms prior to the use of Anovlar® reported improvement or disappearance of their symptoms during the administration of the drug 6.7 per cent stated no change while 22 4 per cent reported an impairment.

Sexual adaptation 45 3 per cent of the women reported improved sexual adaptation during the use of the oral contraceptive. The cause of improvement in 90.6 per cent was stated to be an

Table VII. *Sexual Adaptation During Anovlar®*

Sexual adaptation		No.	%
Improved	Increase of libido	6	2.3
	Increase of security	106	41.1
	Other reasons	5	1.9
Unchanged		74	28.7
Impaired	Decrease of libido	55	21.3
	Dyspareunia	7	2.7
	Other reasons	5	1.9
Total		258	

increased feeling of security. Only 2.3 per cent reported an increase of libido. 26.0 per cent of the sample reported impaired sexual adaptation, the majority of these stating a decrease of libido. The changes in sexual adaptation during Anovlar® medication are shown in Table VII.

Psychological and psychiatric factors. The major part of the questionnaire comprised items regarding psychiatric symptoms and complaints, occurring during the administration of the tablets as well as during the previous year. In answering the items concerning psychiatric symptoms during the use of the drug, the subjects were particularly requested always to state their condition *in relation to the year before* the start of therapy. The items were intended to give information on affective disorders, anxiety, asthenic reactions and sleep disturbances. The results are presented in Table VIII. The last four questions in the table are regarded as unspecific from a psychiatric point of view, and they are excluded from the calculations below. The most frequent symptoms reported were an increase of tiredness, irritability, sensitivity and feeling of depression. Increased sleep disturbances and anxiety symptoms were less frequently reported.

The *number of new or worsened* psychiatric symptoms was calculated for each of the subjects. In Table IX the series is analysed into groups according to the number of such symptoms reported. About 48 per cent of the material reported no new or

Table V *Side Effects Stated to be the Cause of Cessation (91 Subjects)*

Side-effects	%	
Psychiatric symptoms	23.9	43.3
Tiredness	9 7	
Decrease of libido	9 7	
Weight gain	26.1	
Nausea	15.7	
Somatic symptoms	14.9	

Table VI. *Weight Changes During Anovlar® Administration in Relation to Average Weight During the Year Before Use*

Weight change	No.	%
Decrease >5 kg	5	1.9
Decrease 2–5 kg	18	7 0
Unchanged within + – 2 kg	79	30.5
Increase 2–5 kg	106	40 9
Increase >5 kg	41	15.8
Data not available	10	3.9
Total	259	

respectively The frequency of occurrence of a heavy menstrual flow was reduced during administration from 33 5 to 4.2 per cent.

The questionnaire included three items regarding premenstrual tension, namely feeling of distendedness irritability and feeling of depression prior to menstruation. 70 9 per cent of the subjects who had experienced premenstrual tension symptoms prior to the use of Anovlar® reported improvement or disappearance of their symptoms during the administration of the drug. 6 7 per cent stated no change while 22.4 per cent reported an impairment.

Sexual adaptation 45 3 per cent of the women reported improved sexual adaptation during the use of the oral contraceptive. The cause of improvement in 90 6 per cent was stated to be an

Table VII Sexual Adaptation During Anovlar®

Sexual adaptation		No	%
Improved	Increase of libido	6	2.3
	Increase of security	106	41.1
	Other reasons	5	1.9
Unchanged		74	28.7
Impaired	Decrease of libido	55	21.3
	Dyspareuni	7	2.7
	Other reasons	5	1.9
Total		258	

increased feeling of security Only 2.3 per cent reported an increase of libido. 26.0 per cent of the sample reported impaired sexual adaptation, the majority of these stating a decrease of libido The changes in sexual adaptation during Anovlar® medication are shown in Table VII.

Psychological and psychiatric factors. The major part of the questionnaire comprised items regarding psychiatric symptoms and complaints, occurring during the administration of the tablets as well as during the previous year In answering the items concerning psychiatric symptoms during the use of the drug, the subjects were particularly requested always to state their condition *in relation to the year before* the start of therapy The items were intended to give information on affective disorders, anxiety asthenic reactions and sleep disturbances. The results are presented in Table VIII. The last four questions in the table are regarded as unspecific from a psychiatric point of view and they are excluded from the calculations below The most frequent symptoms reported were an increase of tiredness irritability sensitivity and feeling of depression. Increased sleep disturbances and anxiety symptoms were less frequently reported.

The number of new or worsened psychiatric symptoms was calculated for each of the subjects In Table IX the series is analysed into groups according to the number of such symptoms reported About 48 per cent of the material reported no new or

Table V *Side Effects Stated to be the Cause of Cessation (91 Subjects)*

Side-effects	%	
Psychiatric symptoms	23.9	
Tiredness	9.7	43.3
Decrease of libido	9.7	
Weight gain	26.1	
Nausea	15.7	
Somatic symptoms	14.9	

Table VI. *Weight Changes During Anovlar® Administration in Relation to Average Weight During the Year Before Use*

Weight change	No.	%
Decrease >5 kg	5	1.9
Decrease 2–5 kg	18	7.0
Unchanged within ±2 kg	79	30.5
Increase 2–5 kg	100	40.9
Increase >5 kg	41	15.8
Data not available	10	3.9
Total	259	

respectively. The frequency of occurrence of a heavy menstrual flow was reduced during administration from 33.5 to 4.2 per cent.

The questionnaire included three items regarding premenstrual tension, namely feeling of distendedness, irritability and feeling of depression prior to menstruation. 70.9 per cent of the subjects who had experienced premenstrual tension symptoms prior to the use of Anovlar® reported improvement or disappearance of their symptoms during the administration of the drug. 6.7 per cent stated no change, while 22.4 per cent reported an impairment.

Sexual adaptation. 45.3 per cent of the women reported improved sexual adaptation during the use of the oral contraceptive. The cause of improvement in 90.6 per cent was stated to be an

Table IX. *The Distribution of the Subjects According to the Number of New or Worsened Psychiatric Symptoms Reported*

Number of symptoms	No.	%
0	124	47.9
1–2	56	21.6
3–4	26	10.0
≥5	46	17.8
Unanswered	7	2.7
Total	259	

worsened symptoms 32 per cent reported 1–4 symptoms while the remainder about 17 per cent, reported many symptoms, 5–10 When the same calculations were made only for women not reporting any previous psychiatric history (63 women excluded) 55.3 per cent reported no new symptoms during Anovlar® administration, 29.5 per cent reported 1–4 symptoms and 15.0 per cent 5–10 symptoms.

The women were also asked to answer a more generally worded question about their emotional health during use of the tablets. As shown in Table X, about 45 per cent of the subjects reported no emotional disturbances at all, 27 per cent reported no change of existing psychiatric symptoms, 16 per cent reported the appearence or worsening of psychiatric symptoms, while 9 per cent reported an improvement during the oral contraceptive administration. These frequencies are in good accordance with the frequency of reported psychiatric symptoms as is shown in Table IX. This may indicate that there is good consistency between these two methods of questioning. It also indicates that more than one psychiatric symptom is necessary for the subjects to judge their condition as impaired.

The women were also asked about earlier administration of psychopharmacological drugs and earlier visits to a doctor because of nervous complaints. The answers are summarized in Table XI together with reports on psychiatric symptoms during the year before the initiation of the contraceptive medication. About 25 per cent of the subjects mentioned some kind of earlier

Table VIII. *Psychiatric Symptoms During Oral Contraceptive Administration. The + Sign Indicates an Increase or Début of the Symptom the − Sign a Decrease or Disappearence*

Symptom		No.	%
Tiredness	+	71	27.4
	unchanged	158	61.0
	−	22	8.5
Sleep disturbances	+	17	6.6
	unchanged	214	82.6
	−	19	7.3
Irritability	+	73	28.2
	unchanged	151	58.3
	−	26	10.0
Affective instability	+	51	19.7
	unchanged	165	63.7
	−	35	13.5
Sensitivity	+	60	23.2
	unchanged	173	66.8
	−	17	6.6
Emotional incontinence	+	36	13.9
	unchanged	192	74.1
	−	21	8.1
Depression	+	52	20.1
	unchanged	173	66.8
	−	26	10.0
Tension	+	42	16.2
	unchanged	183	70.7
	−	26	10.0
Palpitation	increased	33	12.7
Occasional difficulty in breathing	increased	21	8.1
Headache	+	57	22.0
	unchanged	158	61.0
	−	37	14.3
Sweating	+	58	22.4
	unchanged	183	70.7
	−	11	4.2
Nausea and vomiting	increased	63	24.3
Appetite	+	112	43.2
	unchanged	127	49.0
	−	13	5.0

Table IX. The Distribution of the Subjects According to the Number of New or Worsened Psychiatric Symptoms Reported

Number of symptoms	No.	%
0	124	47.9
1 2	56	21.6
3–4	26	10 0
≥ 5	46	17 8
Unanswered	7	2.7
Total	259	

worsened symptoms, 32 per cent reported 1–4 symptoms, while the remainder about 17 per cent, reported many symptoms 5–10 When the same calculations were made only for women not reporting any previous psychiatric history (63 women ex cluded) 55 3 per cent reported no new symptoms during Anovlar® administration, 29.5 per cent reported 1–4 symptoms and 15.0 per cent 5–10 symptoms

The women were also asked to answer a more generally word ed question about their emotional health during use of the tablets As shown in Table X about 45 per cent of the subjects reported no emotional disturbances at all 27 per cent reported no change of existing psychiatric symptoms 16 per cent reported the appearence or worsening of psychiatric symptoms while 9 per cent reported an improvement during the oral contraceptive administration. These frequencies are in good accordance with the frequency of reported psychiatric symptoms as is shown in Table IX This may indicate that there is good consistency between these two methods of questioning It also indicates that more than one psychiatric symptom is necessary for the subjects to judge their condition as impaired

The women were also asked about earlier administration of psychopharmacological drugs and earlier visits to a doctor because of nervous complaints The answers are summarized in Table XI together with reports on psychiatric symptoms during the year before the initiation of the contraceptive medication. About 75 per cent of the subjects mentioned some kind of earlier

Table VIII. *Psychiatric Symptoms During Oral Contraceptive Administration. The + Sign Indicates an Increase or Début of the Symptom the − Sign a Decrease or Disappearence*

Symptom		No.	%
	+	71	27.4
Tiredness	unchanged	158	61.0
	−	22	8.5
	+	17	6.6
Sleep disturbances	unchanged	214	82.6
	−	19	7.3
	+	73	28.2
Irritability	unchanged	151	58.3
	−	26	10.0
	+	51	19.7
Affective instability	unchanged	165	63.7
	−	35	13.5
	+	60	23.2
Sensitivity	unchanged	173	66.8
	−	17	6.6
	+	36	13.9
Emotional incontinence	unchanged	192	74.1
	−	21	8.1
	+	52	20.1
Depression	unchanged	173	66.8
	−	26	10.0
	+	42	16.2
Tension	unchanged	183	70.7
	−	26	10.0
Palpitation	increased	33	12.7
Occasional difficulty in breathing	increased	21	8.1
	+	57	22.0
Headache	unchanged	158	61.0
	−	37	14.3
	+	58	22.4
Sweating	unchanged	183	70.7
	−	11	4.2
Nausea and vomiting	increased	63	24.3
	+	112	43.2
Appetite	unchanged	127	49.0
	−	13	5.0

Table IX. The Distribution of the Subjects According to the Number of New or Worsened Psychiatric Symptoms Reported

Number of symptoms	No	%
0	124	47.9
1 2	56	21.6
3-4	26	10.0
≥ 5	46	17.8
Unanswered	7	2.7
Total	259	

worsened symptoms, 32 per cent reported 1-4 symptoms while the remainder about 17 per cent, reported many symptoms, 5-10 When the same calculations were made only for women not reporting any previous psychiatric history (63 women excluded) 55.3 per cent reported no new symptoms during Anovlar® administration, 29.5 per cent reported 1-4 symptoms and 15.0 per cent 5-10 symptoms

The women were also asked to answer a more generally worded question about their emotional health during use of the tablets. As shown in Table X, about 45 per cent of the subjects reported no emotional disturbances at all, 27 per cent reported no change of existing psychiatric symptoms 16 per cent reported the appearence or worsening of psychiatric symptoms while 9 per cent reported an improvement during the oral contraceptive administration. These frequencies are in good accordance with the frequency of reported psychiatric symptoms as is shown in Table IX. This may indicate that there is good consistency between these two methods of questioning. It also indicates that more than one psychiatric symptom is necessary for the subjects to judge their condition as impaired.

The women were also asked about earlier administration of psychopharmacological drugs and earlier visits to a doctor because of nervous complaints. The answers are summarized in Table XI together with reports on psychiatric symptoms during the year before the initiation of the contraceptive medication. About 25 per cent of the subjects mentioned some kind of ...

Table VIII. *Psychiatric Symptoms During Oral Contraceptive Administration. The + Sign Indicates an Increase or Début of the Symptom the − Sign a Decrease or Disappearence*

Symptom		No.	%
Tiredness	+	71	27.4
	unchanged	158	61.0
	−	22	8.5
Sleep disturbances	+	17	6.6
	unchanged	214	82.6
	−	19	7.3
Irritability	+	73	28.2
	unchanged	151	58.3
	−	26	10.0
Affective instability	+	51	19.7
	unchanged	165	63.7
	−	35	13.5
Sensitivity	+	60	23.2
	unchanged	173	66.8
	−	17	6.6
Emotional incontinence	+	36	13.9
	unchanged	192	74.1
	−	21	8.1
Depression	+	52	20.1
	unchanged	173	66.8
	−	26	10.0
Tension	+	42	16.2
	unchanged	183	70.7
	−	26	10.0
Palpitation	increased	33	12.7
Occasional difficulty in breathing	increased	21	8.1
Headache	+	57	22.0
	unchanged	158	61.0
	−	37	14.3
Sweating	+	58	22.4
	unchanged	183	70.7
	−	11	4.2
Nausea and vomiting	increased	63	24.3
Appetite	+	112	43.2
	unchanged	127	49.0
	−	13	5.0

Table IX. The Distribution of the Subjects According to the Number of New or Worsened Psychiatric Symptoms Reported

Number of symptoms	No.	%
0	124	47.9
1 2	56	21.6
3–4	26	10.0
≥5	46	17 8
Unanswered	7	2 7
Total	259	

worsened symptoms, 32 per cent reported 1–4 symptoms, while the remainder about 17 per cent, reported many symptoms, 5–10. When the same calculations were made only for women not reporting any previous psychiatric history (63 women ex cluded) 55.3 per cent reported no new symptoms during Anovlar® administration, 29.5 per cent reported 1–4 symptoms and 15.0 per cent 5–10 symptoms.

The women were also asked to answer a more generally worded question about their emotional health during use of the tablets. As shown in Table X, about 45 per cent of the subjects reported no emotional disturbances at all, 27 per cent reported no change of existing psychiatric symptoms 16 per cent reported the appearence or worsening of psychiatric symptoms, while 9 per cent reported an improvement during the oral contraceptive administration. These frequencies are in good accordance with the frequency of reported psychiatric symptoms as is shown in Table IX. This may indicate that there is good consistency between these two methods of questioning. It also indicates that more than one psychiatric symptom is necessary for the subjects to judge their condition as impaired.

The women were also asked about earlier administration of psychopharmacological drugs and earlier visits to a doctor because of nervous complaints. The answers are summarized in Table XI, together with reports on psychiatric symptoms during the year before the initiation of the contraceptive medication. About 25 per cent of the subjects mentioned some kind of earlier

Table X. *Emotional Health During Oral Contraceptive Administration*

	No.	%
No psychiatric symptoms at all	117	45.2
Increase of psychiatric symptoms	41	15.8
No change of psychiatric symptoms	70	27.0
Decrease of psychiatric symptoms	23	8.9
Unanswered	8	3.1
Total	259	

Table XI. *Factors Relating to Earlier Psychiatric History*

	No.	%
Psychiatric symptoms during the year prior to Anovlar® medication	63	24.3
Earlier use of psychopharmaca	66	25.5
Earlier visits to a doctor because of nervous complaints	61	23.6

nervous complaints the degree and extensiveness of which we are unable to judge. No direct comparison of the frequency figures for psychiatric symptoms before and during contraceptive administration was possible because the patients were asked to describe symptoms experienced during medication *in relation to their condition before*.

Correlations. Table XII presents a series of factors and variables correlated to the number of psychiatric symptoms during the oral contraceptive administration (see Table IX).

No significant correlations were found regarding parity, age and social group. Women with a high number of psychiatric symptoms, 5–10, were found to have discontinued the contraceptive medication significantly earlier. They also reported to a significantly greater extent previous psychiatric symptoms and

Presentation of the correlations in tabular form is not possible due to limitations of space.

Table XII. *Correlations Between the Individual Number of Psychiatric Symptoms During the Oral Contraceptive Administration (see Table IX) and Other Variables*

Variable	χ^2	df	p
Age	1.00	4	N.S
Parity	1.80	2	N.S
Social group	6.93	6	N.S.
Weight gain >5 kg during medication	8.61	2	<0.02
Duration of oral contraceptive administration	14.77	2	<0.001
Psychiatric symptoms prior to medication	17.24	4	<0.01
Use of psychopharmaca prior to medication	23.33	2	<0.001
Emotional disturbances during earlier pregnancy	21.93	2	<0.001
Nausea and vomiting during earlier pregnancy	13.32	2	<0.01
Premenstrual tension symptoms during oral contraceptive administration	34.00	2	<0.001
Sexual adaptation during oral contraceptive administration	46.87	4	<0.001
Validity	10.41	2	<0.01
Stability	1.10	2	N.S.
Solidity	1.52	2	N.S

previous use of psychopharmacological drugs. Furthermore they stated a significantly higher frequency of impaired sexual adaptation, i.e. a decrease of libido. They were also found to experience an increase of premenstrual tension symptoms. Reported mental disturbances as well as nausea and vomiting during earlier pregnancy or pregnancies were significantly related to an increased number of psychiatric symptoms during the oral contraceptive administration. Weight increase of more than 5 kg was significantly related to an increased number of psychiatric symptoms but no relation was found between psychiatric symptoms and a moderate weight gain (2.5 kg). There were no relationship between the number of psychiatric symptoms and the dimensions of stability and solidity according to the personality inventory the MNT-scale. A significant relationship was found between a high number of psychiatric symptoms and subvalidity. The questions of the validity scale are intended to measure the general capacity for energetic investment and recovery, for instance in

Table X. *Emotional Health During Oral Contraceptive Administration*

	No.	%
No psychiatric symptoms at all	117	45.2
Increase of psychiatric symptoms	41	15.8
No change of psychiatric symptoms	70	27.0
Decrease of psychiatric symptoms	23	8.9
Unanswered	8	3.1
Total	259	

Table XI. *Factors Relating to Earlier Psychiatric History*

	No.	%
Psychiatric symptoms during the year prior to Anovlar® medication	63	24.3
Earlier use of psychopharmaca	66	25.5
Earlier visits to a doctor because of nervous complaints	61	23.6

nervous complaints the degree and extensiveness of which we are unable to judge No direct comparison of the frequency figures for psychiatric symptoms before and during contraceptive administration was possible because the patients were asked to describe symptoms experienced during medication *in relation to their condition before*

Correlations Table XII presents a series of factors and variables correlated to the number of psychiatric symptoms during the oral contraceptive administration (see Table IX)

No significant correlations were found regarding parity age and social group Women with a high number of psychiatric symptoms, 5–10 were found to have discontinued the contraceptive medication significantly earlier They also reported to a significantly greater extent previous psychiatric symptoms and

Presentation of the correlations in tabular form is not possible due to limitations of space.

and affective instability. Increase of nausea and vomiting, impairment of sexual adaptation and a weight gain of more than 5 kg were also significantly associated with an earlier cessation. No significant relationship was found between cessation and a moderate weight gain (2–5 kg), tachycardia, breathing difficulties, sleep disturbances or increased perspiration. Nor were there any significant relations between previous psychiatric symptoms or previous use of psychopharmaca and cessation of the medication. Subjects registered as subsolid according to the MNT-scale discontinued the oral contraceptive administration earlier to a significantly greater degree. The items of solidity scale are related to long range organization of actions. The subsolid individual is regarded to prefer change and excitement, to make sudden decisions, to be impulsive and to act on the spur of the moment.

When correlating the three groups of sexual adaptation (cf Table VII) with other factors, significant relations were found between impaired sexual adaptation, i.e. mainly a decrease of libido on the one hand and an increased number of reported psychiatric symptoms ($p < 0.001$), earlier cessation ($p < 0.01$) and weight gain of more than 5 kg ($p < 0.01$) on the other. No significant relationship was found between sexual adaptation during the use of the contraceptive and parity, changes of premenstrual tension symptoms and psychiatric symptoms or periods of illness prior to the medication.

As mentioned above, women reporting an increase of premenstrual tension symptoms during use of the drug mentioned an increased number of psychiatric symptoms to a greater extent and also discontinued administration of the tablets earlier. A further strongly significant relationship was found between an increase of premenstrual tension symptoms during the contraceptive medication and nausea and vomiting during earlier pregnancy or pregnancies ($p < 0.001$). Weight gain of more than 5 kg was also more often found among these subjects ($p < 0.01$). There was no relationship between premenstrual tension and psychiatric symptoms prior to the administration of the tablets.

Weight gain of more than 5 kg during the use of the tablets was significantly related to an increased number of new or

Table XIII *Correlations Between Continued—Discontinued Medication and Different Variables*

Variable	z	d.f.	p
No. of psychiatric symptoms during Anovlar® medication	14.77	2	<0.001
Depression	16.40	2	<0.001
Tiredness	22.47	2	<0.001
Sensitivity	18.13	2	<0.001
Emotional instability	21.40	2	<0.001
Irritability	10.19	2	<0.01
Affective instability	6.49	2	<0.05
Tension	8.34	2	<0.02
Sleep disturbances	2.59	1	N.S.
Palpitations	0.45	1	N.S.
Occasional difficulty in breathing	0.83	1	N.S.
Sweating	0.18	1	N.S.
Nausea and vomiting	21.49	1	<0.001
Sexual adaptation	9.55	2	<0.01
Weight changes	6.60	2	<0.05
Earlier psychiatric symptoms	0.05	1	N.S.
Earlier use of psychopharmaca	1.57	1	N.S.
Validity	2.46	1	N.S.
Stability	0.16	1	N.S.
Solidity	7.78	1	<0.05

connection with new situations and tasks demanding a certain flexibility or readjustment. Thus the subvalid individuals rate themselves as being less effective in these respects. A relation has earlier been found between subvalidity and neuroticism (*Nyman* and *Marke* 1961, *Marke* 1963).

Correlations were made concerning different factors between women still using the contraceptive at the time of investigation and those having already discontinued (Table XIII).

As mentioned above, subjects with a high number of new or worsened psychiatric symptoms during the use of the drug had to a larger extent discontinued the tablets. Feeling of depression, tiredness, sensitivity and emotional incontinence were the symptoms most strongly associated with cessation. Earlier cessation was also significantly related to increased irritability, tension

and affective instability. Increase of nausea and vomiting, impairment of sexual adaptation and a weight gain of more than 5 kg were also significantly associated with an earlier cessation. No significant relationship was found between cessation and a moderate weight gain (2-5 kg) tachycardia, breathing difficulties, sleep disturbances or increased perspiration. Nor were there any significant relations between previous psychiatric symptoms or previous use of psychopharmaca and cessation of the medication. Subjects registered as subsolid according to the MNT-scale discontinued the oral contraceptive administration earlier to a significantly greater degree. The items of solidity scale are related to long range organization of actions. The subsolid individual is regarded to prefer change and excitement, to make sudden decisions, to be impulsive and to act on the spur of the moment.

When correlating the three groups of sexual adaptation (cf Table VII) with other factors, significant relations were found between impaired sexual adaptation, i.e. mainly a decrease of libido on the one hand and an increased number of reported psychiatric symptoms ($p < 0.001$) earlier cessation ($p < 0.01$) and weight gain of more than 5 kg ($p < 0.01$) on the other. No significant relationship was found between sexual adaptation during the use of the contraceptive and parity changes of premenstrual tension symptoms and psychiatric symptoms or periods of illness prior to the medication.

As mentioned above, women reporting an increase of premenstrual tension symptoms during use of the drug mentioned an increased number of psychiatric symptoms to a greater extent and also discontinued administration of the tablets earlier. A further strongly significant relationship was found between an increase of premenstrual tension symptoms during the contraceptive medication and nausea and vomiting during earlier pregnancy or pregnancies ($p < 0.001$). Weight gain of more than 5 kg was also more often found among these subjects ($p < 0.01$). There was no relationship between premenstrual tension and psychiatric symptoms prior to the administration of the tablets.

Weight gain of more than 5 kg during the use of the tablets was significantly related to an increased number of new or

Table XIII. *Correlations Between Continued—Discontinued Medication and Different Variables*

Variable	χ^2	d.f.	p
No of psychiatric symptoms during Anovlar® medication	14.77	2	<0.001
Depression	16.40	2	<0.001
Tiredness	22.47	2	<0.001
Sensitivity	18.13	2	<0.001
Emotional instability	21.40	2	<0.001
Irritability	10.19	2	<0.01
Affective instability	6.49	2	<0.05
Tension	8.34	2	<0.02
Sleep disturbances	2.59	1	N.S.
Palpitations	0.45	1	N.S.
Occasional difficulty in breathing	0.83	1	N.S.
Sweating	0.18	1	N.S.
Nausea and vomiting	21.49	1	<0.001
Sexual adaptation	9.55	2	<0.01
Weight changes	6.60	2	<0.05
Earlier psychiatric symptoms	0.05	1	N.S
Earlier use of psychopharmaca	1.57	1	N.S
Validity	2.46	1	N.S.
Stability	0.16	1	N.S.
Solidity	7.78	1	<0.05

connection with new situations and tasks demanding a certain flexibility or readjustment. Thus the subvalid individuals rate themselves as being less effective in these respects. A relation has earlier been found between subvalidity and neuroticism (*Nyman* and *Marke* 1961 *Marke* 1963)

Correlations were made concerning different factors between women still using the contraceptive at the time of investigation and those having already discontinued (Table XIII)

As mentioned above subjects with a high number of new or worsened psychiatric symptoms during the use of the drug had to a larger extent discontinued the tablets Feeling of depression, tiredness sensitivity and emotional incontinence were the symptoms most strongly associated with cessation Earlier cessation was also significantly related to increased irritability tension

n connection with the use of the oral contraceptive are con erned, such comparisons have always been made between the ondition before and during treatment. This fact in addition to he retrospective nature of the investigation, might imply a loss of information due to for example failure of memory In addition, where the patients answered questions about experiences before the investigation was made, events in the intervening period may have influenced the intensity of their impressions of various symptoms. The use of a questionnaire for the investigation implies the risk that some questions may be misunderstood or misinterpreted. It is not possible to obtain such precise answers as in a personal interview On the other hand, because of the standardization of our method, the halo effect which may occur in a personal interview is avoided. The design and nature of the questionnaire and the actual questions can of course themselves influence a reply in a certain direction. A low frequency of replies can further prejudice the reliability of the results obtained.

One source of error to be considered in this investigation is the possibility that a number of women with psychiatric illness unconnected with the use of the oral contraceptive tablets, as well as habitually neurotic women may have blamed their symptoms on the tablets.

Despite the occurrence of bias factors, we nevertheless believe that our results reflect actual conditions and throw light on problems which may be of clinical importance. Of course, the results are representative only of the type of women who were prescribed the tablets at this Hospital during 1964 but we feel that the inferences from this study have a wider applicability

As already mentioned, we have taken great care in the formulation of the questions since it is clear that this is of great importance for comprehension and readiness to answer The high frequency of replies 91 0 per cent, and the very small internal loss of unanswered questions suggest that the interest and motivation to cooperate was very good. We would further emphasize that in the design of the questions we have tried to avoid the impression that only negative side-effects were of interest. From earlier experience with a similar technique (*Jacobson* Kalj and Nilsson 1965) we know that a relatively large

worsened psychiatric symptoms (Table XII) No significant relationship between weight gain and psychiatric symptoms prior to the oral contraceptive administration was found, although there was a trend ($Chi^2 = 9.24$ 4 d.f., N.S.) On the other hand, women with a previous administration of psychopharmaca reported weight gain, moderate and considerable, to a greater extent ($p < 0.01$) This will be further discussed. Weight change was not related to age and parity

The standard weight and the deviations from this before the start of oral contraceptive treatment was calculated for each woman. Women above standard weight were to a significantly greater degree found to show a weight gain during Anovlar® medication ($p < 0.001$) No relationship between deviation from the standard weight and psychiatric symptoms during or prior to the use of the tablets was found.

Finally a comparison was made between women who were prescribed the oral contraceptive for contraception and those with endometriosis. It must be borne in mind that the endometriosis group is rather small only 22 subjects. No significant differences regarding psychiatric symptoms weight changes and the sexual adaptation during Anovlar® administration were found. Neither were any differences found between the groups regarding previous psychiatric symptoms Women with endometriosis were to some extent older and they had significantly fewer pregnancies, 50 per cent being nulliparous

Discussion

The results of this type of investigation must be judged with care and with due regard for errors inherent in the method Because of the nature of the investigation, there is no control group—for instance the questionnaire would be inappropriate for patients using diaphragms or IUCD—thus it has only been possible to make comparisons within the sample Where changes

The standard weight deviations were calculated from standard weight tables according to Prof H. Natvig. Deviations of more than + − 10 per cent from the calculated standard weight were registered as overweight and under weight respectively (13)

in connection with the use of the oral contraceptive are concerned, such comparisons have always been made between the condition before and during treatment. This fact in addition to the retrospective nature of the investigation, might imply a loss of information due to, for example, failure of memory. In addition, where the patients answered questions about experiences before the investigation was made, events in the intervening period may have influenced the intensity of their impressions of various symptoms. The use of a questionnaire for the investigation implies the risk that some questions may be misunderstood or misinterpreted. It is not possible to obtain such precise answers as in a personal interview. On the other hand, because of the standardization of our method, the halo effect which may occur in a personal interview is avoided. The design and nature of the questionnaire and the actual questions can of course themselves influence a reply in a certain direction. A low frequency of replies can further prejudice the reliability of the results obtained.

One source of error to be considered in this investigation is the possibility that a number of women with psychiatric illness unconnected with the use of the oral contraceptive tablets, as well as habitually neurotic women, may have blamed their symptoms on the tablets.

Despite the occurrence of bias factors, we nevertheless believe that our results reflect actual conditions and throw light on problems which may be of clinical importance. Of course, the results are representative only of the type of women who were prescribed the tablets at this Hospital during 1964 but we feel that the inferences from this study have a wider applicability.

As already mentioned, we have taken great care in the formulation of the questions since it is clear that this is of great importance for comprehension and readiness to answer. The high frequency of replies, 91.0 per cent, and the very small internal loss of unanswered questions suggest that the interest and motivation to cooperate was very good. We would further emphasize that in the design of the questions we have tried to avoid the impression that only negative *side-effects* were of interest. From earlier experience with a similar technique (*Jacobson, Kalf* and *Nilsson* 1965) we know that a relatively large

worsened psychiatric symptoms (Table XII) No significant relationship between weight gain and psychiatric symptoms prior to the oral contraceptive administration was found although there was a trend ($Chi^2 = 9.24$ 4 d.f N.S.) On the other hand, women with a previous administration of psychopharmaca reported weight gain, moderate and considerable to a greater extent ($p < 0.01$) This will be further discussed. Weight change was not related to age and parity

The standard weight and the deviations from this before the start of oral contraceptive treatment was calculated for each woman. Women above standard weight were to a significantly greater degree found to show a weight gain during Anovlar® medication ($p < 0.001$) No relationship between deviation from *the standard weight and psychiatric symptoms during or prior* to the use of the tablets was found.

Finally a comparison was made between women who were prescribed the oral contraceptive for contraception and those with endometriosis. It must be borne in mind that the endometriosis group is rather small only 22 subjects. No significant differences regarding psychiatric symptoms weight changes and the sexual adaptation during Anovlar® administration were found. Neither were any differences found between the groups regarding previous psychiatric symptoms. Women with endometriosis *were to some extent older and they had significantly fewer pregnancies* 50 per cent being nulliparous

Discussion

The results of this type of investigation must be judged with care and with due regard for errors inherent in the method. Because of the nature of the investigation, there is no control group—for instance, the questionnaire would be inappropriate for patients using diaphragms or IUCD—thus it has only been possible to make comparisons within the sample Where changes

The standard weight deviation were calculated from standard weight tables according to Prof H. Natvig Deviations of more than + − 10 per cent from the calculated standard weight were registered as overweight and underweight respectively (13)

in connection with the use of the oral contraceptive are concerned, such comparisons have always been made between the condition before and during treatment. This fact in addition to the retrospective nature of the investigation, might imply a loss of information due to for example, failure of memory In addition, where the patients answered questions about experiences before the investigation was made, events in the intervening period may have influenced the intensity of their impressions of various symptoms. The use of a questionnaire for the investigation implies the risk that some questions may be misunderstood or misinterpreted. It is not possible to obtain such precise answers as in a personal interview On the other hand, because of the standardization of our method, the halo effect which may occur in a personal interview is avoided. The design and nature of the questionnaire and the actual questions can of course themselves influence a reply in a certain direction. A low frequency of replies can further prejudice the reliability of the results obtained.

One source of error to be considered in this investigation is the possibility that a number of women with psychiatric illness unconnected with the use of the oral contraceptive tablets as well as habitually neurotic women, may have blamed their symptoms on the tablets.

Despite the occurrence of bias factors we nevertheless believe that our results reflect actual conditions and throw light on problems which may be of clinical importance. Of course, the results are representative only of the type of women who were prescribed the tablets at this Hospital during 1964 but we feel that the inferences from this study have a wider applicability

As already mentioned, we have taken great care in the formulation of the questions since it is clear that this is of great importance for comprehension and readiness to answer The high frequency of replies, 91 0 per cent, and the very small internal loss of unanswered questions suggest that the interest and motivation to cooperate was very good. We would further emphasize that in the design of the questions we have tried to od the impression that only negative side-effects were of interest From earlier experience with a similar technique (*Jacobson Kall and Nilsson 1965*) we know that a relatively large

number of questions can be posed without influencing the frequency of replies

One source of error the size and importance of which we have been unable to estimate is the influence of more or less accurate reports on side-effects in the mass media. Many of those women who had in fact never began to use the tablets mentioned fear of side-effects as the reason. It should, however, be pointed out that hardly any reports of *psychiatric* side-effects had appeared before this investigation was commenced.

We are unable to state the proportions of habitually neurotic women or women with earlier or present emotional disorders unconnected with the oral contraception which have blamed their symptoms on the tablets However for the following reasons we believe these proportions to be relatively small If the reply frequencies had been influenced to an appreciable extent by projective mechanisms a higher frequency of answers regarding sleep disturbances and anxiety symptoms than we have found (Table VIII) would be expected, since such symptoms are common in neurotic patients Furthermore, one would not expect positive effects on, for example, dysmenorrhoea and premenstrual tension to be reported to such a wide extent if the results were strongly influenced by replies from habitually neurotic individuals Our comparisons between women who were prescribed Anovlar® purely as a contraceptive and those who were prescribed the tablets for the treatment of endometriosis are uncertain since there is a large difference in the size of the two groups. Nevertheless it appears that there are no large differences in frequency of side-effects This supports our view that the frequencies obtained are not significantly influenced by psychological or external factors such as the use of the preparation as a contraceptive *per se* or reports of side-effects in mass media

About 15 per cent of the women stated psychiatric or sexual changes as the cause of cessation of treatment They had to a large extent returned to mechanical or chemical contraception at the time of investigation (that is within 1¼–2¼ years) Further 20 per cent of the sample had discontinued because of other side-effects (weight gain, nausea and other somatic symptoms) This indicates that the use of the oral contraceptive has in many cases

implied disadvantages which outweigh the increased contraceptive security

If the number of psychiatric symptoms *stated* is used as a criterion of morbidity we find that the number of women with a début or marked increase of symptoms during the use of the oral contraceptive is about 17 per cent (cf Table IX) In addition a rather large group of women stated a small or moderate number of such symptoms. The increase of symptoms was moreover investigated in another way using a more openly designed question in which the women were asked to state whether they had ever experienced nervous complaints and, if so whether these had improved, worsened or remained unchanged during treatment. We find a good agreement between the two approaches, each giving a 16 to 17 per cent increase of symptoms (cf Table IX and X) The frequencies in our survey are of the same order as those given by Hauser (*Hauser* and *Schubiger* 1965) The frequencies for the increase of individual psychiatric symptoms during Anovlar® treatment show a wide variation. Our questionnaire does not enable psychiatric diagnoses, but the most common symptoms reported were those of a neurasthenic or depressive nature tiredness, irritability increased sensitivity and a feeling of depression. In a prospective study of mental symptoms during pregnancy and the post partum period one of us (A. Nilsson) has observed that this group of symptoms is very common during early pregnancy The comparison is interesting, the more so since in the present material there is a significant relationship between an increase of psychiatric symptoms during oral contraception and psychiatric symptoms during earlier pregnancy or pregnancies Our method does not enable us to establish the intensity or degree of impairment from the increase in symptoms experienced That the symptoms have in many cases been pronounced is, however indirectly reflected by the strong correlation between an increased number of psychiatric symptoms and an earlier cessation of treatment. The correlation between individual psychiatric symptoms and an earlier cessation of treatment is strongest for the symptoms of neurasthenic and depressive nature Because of the design of the study we are unable to judge the point of time when psychiatric symptoms occurred

number of questions can be posed without influencing the frequency of replies.

One source of error the size and importance of which we have been unable to estimate is the influence of more or less accurate reports on side-effects in the mass media. Many of those women who had in fact never began to use the tablets mentioned fear of side-effects as the reason. It should, however be pointed out that hardly any reports of *psychiatric* side-effects had appeared before this investigation was commenced

We are unable to state the proportions of habitually neurotic women or women with earlier or present emotional disorders unconnected with the oral contraception which have blamed their symptoms on the tablets However for the following reasons we believe these proportions to be relatively small If the reply frequencies had been influenced to an appreciable extent by projective mechanisms a higher frequency of answers regarding sleep disturbances and anxiety symptoms than we have found (Table VIII) would be expected, since such symptoms are common in neurotic patients Furthermore, one would not expect positive effects on, for example dysmenorrhoea and premenstrual tension, to be reported to such a wide extent if the results were strongly influenced by replies from habitually neurotic individuals Our comparisons between women who were prescribed Anovlar® purely as a contraceptive and those who were prescribed the tablets for the treatment of endometriosis are uncertain, since there is a large difference in the size of the two groups. Nevertheless it appears that there are no large differences in frequency of side-effects This supports our view that the frequencies obtained are not significantly influenced by psychological or external factors such as the use of the preparation as a contraceptive *per se* or reports of side-effects in mass media.

About 15 per cent of the women stated psychiatric or sexual changes as the cause of cessation of treatment They had to a large extent returned to mechanical or chemical contraception at the time of investigation (that is within 1¼–2¼ years) Further 20 per cent of the sample had discontinued because of other side-effects (weight gain nausea and other somatic symptoms) This indicates that the use of the oral contraceptive has in many cases

creased appetite during treatment is reported in 43 per cent of the sample. It is, however unlikely that the high frequency of weight gain in our series is entirely due to such factors. Because of the relationship between weight gain and increase of premenstrual tension during treatment fluid retention seems to play a part. The very high correlation between overweight before treatment and weight gain during treatment is not readily explained, but should be taken into account when prescribing the drug. One explanation may be that overweight women are less concerned about their weight. It is only natural that a great increase in weight during treatment was a significant reason for its cessation. A slight weight gain (2–5 kg) however did not produce earlier cessation.

SUMMARY AND CONCLUSIONS

The results of this survey suggest that side-effects of a psychiatric nature are almost as common as purely somatic symptoms and that in many cases their intensity is sufficiently great to motivate earlier cessation of the oral contraceptive treatment. Amongst the individual symptoms, those of a neurasthenic or depressive character were the most common encountered. The frequency of psychiatric side-effects is not related to age, parity marital state or social class.

The study of correlations has enabled us to distinguish some groups of women who appear more sensitive than others as regards the occurrence of psychiatric symptoms during oral contraceptive treatment. Women with a previous history of psychiatric symptoms or insufficiency and women who had experienced emotional problems or severe nausea and vomiting during an earlier pregnancy or pregnancies, to a greater extent reported psychiatric symptoms during treatment. Women who were significantly overweight at the start of treatment tended to react to the medication more unfavourably than others in respect of both weight gain and the experience of psychiatric symptoms. Individuals recorded on the MNT personality scale as subvalid, who may be regarded from a clinical viewpoint as asthenic, were more liable to report psychiatric symptoms.

From a practical, clinical viewpoint, it seems advisable that

or became accentuated, but the relation between increase of these symptoms and early cessation suggests that it is early in medication. Neither is it possible to estimate the duration of the symptoms reported.

Women with previous psychiatric history reported a higher increase of psychiatric symptoms during Anovlar® treatment, but as has been mentioned earlier the frequency of psychiatric symptoms is only slightly lower in women without such a previous history The explanation for the increased frequency of psychiatric symptoms in this group may be that women with an earlier psychiatric burden are more likely to note an increase of psychiatric symptoms which oral contraception may produce It should be noted that an earlier psychiatric history does not in itself imply earlier cessation of treatment but that this only occurs when the symptoms become accentuated during treatment

Impairment of sexual adaptation, principally a decrease of libido was stated by about 25 per cent of the subjects to have occurred during the use of the contraceptive tablets. The frequency of changes in libido is disputed in the literature. Increased libido has been reported in frequencies of 1 4 to 50 per cent and decreased libido in 1 to 25 per cent (*Hauser* and *Schubiger*, 1965 *Ringrose* 1965 *Mears* and *Grant* 1962) The strong association between a high number of psychiatric symptoms and a decreased libido is not unexpected since sexual problems are most often of emotional nature Women who mentioned an impairment of sexual adaptability also discontinued the treatment significantly earlier An earlier psychiatric history did not appear to affect sexual adaptability during treatment

Increase in weight was widely mentioned in our series. 16 per cent stated a marked weight increase of over 5 kg The correlation between weight gain and an increase of psychiatric symptoms is not unexpected. Neither is it surprising that there is a relation between weight gain and previous psychiatric symptoms or the previous use of psychopharmaca since there is a correlation between these variables and increase of psychiatric symptoms during treatment. It is well established that emotional difficulties may induce nervous eating, and that psychopharmaca sometimes produce an increase in weight As shown in Table VIII an in-

creased appetite during treatment is reported in 43 per cent of the sample It is however unlikely that the high frequency of weight gain in our series is entirely due to such factors. Because of the relationship between weight gain and increase of pre-menstrual tension during treatment fluid retention seems to play a part. The very high correlation between overweight before treatment and weight gain during treatment is not readily explained, but should be taken into account when prescribing the drug. One explanation may be that overweight women are less concerned about their weight. It is only natural that a great increase in weight during treatment was a significant reason for its cessation. A slight weight gain (2–5 kg) however did not produce earlier cessation

SUMMARY AND CONCLUSIONS

The results of this survey suggest that side-effects of a psychiatric nature are almost as common as purely somatic symptoms and that in many cases their intensity is sufficiently great to motivate earlier cessation of the oral contraceptive treatment. Amongst the individual symptoms those of a neurasthenic or depressive character were the most common encountered. The frequency of psychiatric side-effects is not related to age, parity marital state or social class.

The study of correlations has enabled us to distinguish some groups of women who appear more sensitive than others as regards the occurrence of psychiatric symptoms during oral contraceptive treatment. Women with a previous history of psychiatric symptoms or insufficiency and women who had experienced emotional problems or severe nausea and vomiting during an earlier pregnancy or pregnancies, to a greater extent reported psychiatric symptoms during treatment Women who were significantly overweight at the start of treatment tended to react to the medication more unfavourably than others in respect of both weight gain and the experience of psychiatric symptoms. Individuals recorded on the MNT personality scale as subvalid, who may be regarded from a clinical viewpoint as asthenic were more liable to report psychiatric symptoms

From a practical, clinical viewpoint, it seems advisable that

oral contraceptives should be more carefully prescribed to women falling into these categories. Furthermore, when patients are encountered who complain of mental symptoms and are also using oral contraceptives, the possibility of a causal connection deserves closer attention

This investigation has yielded a number of positive results which should not be forgotten or overlooked. In addition to the particularly favourable effects on premenstrual tension and dysmenorrhoea, which have been reported previously the increased sense of security led to an improvement of sexual adaptability for about 50 per cent of the women. Furthermore about 9 per cent claimed improvement in previous psychiatric symptoms which, as far as we could judge was connected with increased security on the sexual plane.

This investigation includes only women who have used the preparation Anovlar® AG Schering. There seems, however no reason to believe that other preparations with the same or a similar chemical composition would give appreciably different results Our clinical impression of other preparations does not suggest that any significant differences exist.

REFERENCES

Andersson A. L. Scand. J Psychol 3 205 1962
Bakker C. B. and *Dightman C R.* Obst. Gynec. 28 373 1966
FDA. Report of the oral contraceptives 1966
Hauser G A. and Schubiger V Arch Gynäk. 202 175 1965
Jacobson L. Kaij L. and *Nilsson A.* Brit med. J 1 1640 1965
Kaye B. M J.A.M.A. 186 522, 1963
La Gravinese N Policlinico 72 1639 1965
Lindberg, W., Natvig, H Rygh A and *Svendsen K* Tidsskrift for Den Norske Laegeforening 76 361 1956
Linthorst G Intern J Fertility 11 35 1966
Marke S Socialmedicinsk Tidskr 40 287 1963
Mears E. and *Grant E. C* Brit. med. J 1 75 1962
Nyman G. E. Variations in personality Lund. Berling, 1956
Nyman G E. and *Marke S* Sjöbrings differentiella psykologi. Lund. Gleerup, 1961
Ringrose C. A. D Canad. Med. Ass. J 92 1207 1965
Sjöbring, H Struktur och utveckling. Lund Gleerup 1958
Zell J R. and *Crisp W E.* Obst. Gynec. 23 657 1964

Received on March 20th 1967

Larsson-Cohn, Ulf, Acta obst et gynec scandinav 46, 557 1967

From the Department of Obstetrics and Gynaecology University Hospital (Professor Carl Gemzell) Uppsala, Sweden

FREQUENCY OF BLEEDING IRREGULARITIES WITH TWO COMBINATIONS OF NORETHINDRONE AND MESTRANOL

BY

ULF LARSSON-COHN

Norethindrone is widely used in oral contraceptive agents. The first commercially available drug contained 10 mg of the substance. The dose was however soon reduced, and today a mixture of 2 mg norethindrone and 0 1 mg mestranol/ethinylestradiol-3-methylether/ (Norinyl®, Orthonovin®, Conluten®) is widely used with good clinical results.

During 1966 a combination of norethindrone 1 mg and mestranol 0.05 mg (Norinyl 1®) was marketed in Canada and Great Britain. At the University Hospital in Uppsala this combination was used as an oral contraceptive during 921 cycles. Because of an extremely high incidence of bleeding irregularities the estrogen content was later increased to 0.1 mg. This is a preliminary report of the frequencies of bleeding irregularities.

Material and method

A combination of norethindrone 1 mg and mestranol 0 05 mg was given to 102 women. Because of the high incidence of break-through bleeding and spotting, the dosage of mestranol was increased to 0 1 mg after some months, making a second group of 69 patients. Those patients who changed from the lower to the higher dosage of mestranol were not included in the second group. The majority of the patients were unmarried university students.

All tablets were supplied free of charge. They were dispensed

oral contraceptives should be more carefully prescribed to women falling into these categories Furthermore when patients are encountered who complain of mental symptoms and are also using oral contraceptives the possibility of a causal connection deserves closer attention.

This investigation has yielded a number of positive results which should not be forgotten or overlooked. In addition to the particularly favourable effects on premenstrual tension and dysmenorrhoea, which have been reported previously the increased sense of security led to an improvement of sexual adaptability for about 50 per cent of the women. Furthermore about 9 per cent claimed improvement in previous psychiatric symptoms which, as far as we could judge was connected with increased security on the sexual plane

This investigation includes only women who have used the preparation Anovlar® AG Schering There seems, however no reason to believe that other preparations with the same or a similar chemical composition would give appreciably different results Our clinical impression of other preparations does not suggest that any significant differences exist.

REFERENCES

Andersson A. L., Scand. J Psychol. *3* 205 1962

Bakker C. B. and *Dightman C R.* Obst. Gynec. *28* 373 1966

FDA. Report of the oral contraceptives 1966

Hauser G A. and Schubiger V Arch. Gynäk. *20?* 175 1965

Jacobson L. Kalj L. and *Nilsson A* Brit med. J *1* 1640 1965

Kaye B. M J.A.M.A. *186* 522, 1963

La Gravinese N Policlinico *72* 1639 1965

Lindberg, W Natvig, H Rygh A and *Svendsen K.* Tidsskrift for Den Norske Laegeforening. *76* 361 1956

Linthorst G Intern. J Fertility *11* 35 1966

Marke S., Socialmedicinsk Tidskr *40* 287 1963

Mears E., and *Grant E. C.* Brit. med. J *1* 75 1962

Nyman G E. Variations in personality Lund. Berling, 1956

Nyman G E. and *Marke S* Sjöbrings differentiella psykologi. Lund. Gleerup 1961

Ringrose C. A. D Canad. Med. Ass J *92* 1207 1965

Sjöbring, H Struktur och utveckling. Lund Gleerup 1958

Zell J R. and *Crisp W E.* Obst. Gynec. 23 657 1964

Received on March 20th, 1967

Table II. Incidence of Break-Through Bleeding, Spotting and Amenorrhoea.

Norethindrone 1 mg + mestranol 0.05 mg				Norethindrone 1 mg + mestranol 0.1 mg		
Cycle No	No. of cycles	Cycles with break through bleeding or spotting	Cycles with amenorrhoea	N of cycles	Cycles with break through bleeding or spotting	Cycles with amenorrhoea
1	102	77	2	69	19	2
2	94	44	4	63	10	
3	92	40	4	62	6	
4	89	33	1	47	1	
5	88	26	3	43	3	
6	86	19	5	31	3	
7	81	24	8	20	1	
8	77	18	9	13		
9	66	7	3	3		
10	53	10	3	1		
11	41	4	3			
12	25	3	2			
13	17	1	2			
14	8	2				
15		1				
Totals	921	319	50	352	43	2

the same as was earlier found with tablets containing norethindrone 2 mg and mestranol 0.1 mg.

A summary of co-operative clinical trials of norethindrone 1 mg combined with mestranol 0.05 mg described 3112 subjects who had used the drug for 20,692 cycles without any pregnancy (Syntex 1966). The frequency of break-through bleeding and spotting, 21.8 per cent during the first cycle fell progressively to 4 per cent after the sixth.

Employing the same dosage the frequency of break-through bleeding and spotting in this trial was 75 per cent initially and 22 per cent after six months of treatment. The latter percentage would have been still higher if not a considerable part of the patients with frequent break-through bleedings had been switched over to the tablets containing 0.1 mg estrogen. Amenorrhoea

Table I. *Age Distribution of Patients*

Age in Years	Number of Patients on	
	norethindrone 1 mg + mestranol 0 05 mg	norethindrone 1 mg + mestranol 0 1 mg
16–19	24	21
20–29	61	38
30–39	16	7
40–46	1	3

in special packages each containing 21 tablets each tablet labelled with one of 21 consecutive week-days One tablet was taken daily with 7 day interval between courses of treatment. The participants were provided with printed cards on which to record patterns of treatment and bleeding.

Table I shows the age distribution of the patients in the two groups

Results

No pregnancy occurred among the patients who took the tablets according to instructions while one woman who used the drug with the lower estrogen content conceived after she had omitted two tablets consecutively in the middle of her second cycle of therapy

Table II gives details of abnormal bleeding in both groups of patients Fig 1 shows the incidence of break through bleeding and spotting with 3 different drugs the two used in this trial and a third from an earlier trial with tablets containing norethindrone 2 mg and mestranol 0 1 mg (*Larsson-Cohn* 1964)

Thirteen out of the 102 patients on the low estrogen dosage and 45 out of the 69 on the higher dosage of estrogen reported no irregular bleeding.

Discussion

This study showed that mestranol 0 05 mg with norethindrone 1 mg was totally effective as a contraceptive but insufficient to maintain a good cycle control However by doubling the amount of estrogen, the frequency of bleeding irregularities become about

Table II. *Incidence of Break-Through Bleeding, Spotting and Amenorrhoea.*

	Norethindrone 1 mg + mestranol 0.05 mg			Norethindrone 1 mg + mestranol 0.1 mg		
Cycle No	No. of cycles	Cycles with break-through bleeding or spotting	Cycles with amenor rhoea	No. of cycles	Cycles with break through bleeding or spotting	Cycles with amenor rhoea
1	102	77	2	69	19	2
2	94	44	4	63	10	
3	92	40	4	62	6	
4	89	33	1	47	1	
5	88	28	3	43	3	
6	86	19	5	31	3	
7	81	24	8	20	1	
8	77	18	9	13		
9	66	17	3	3		
10	53	10	3	1		
11	41	4	3			
12	25	3	2			
13	17	1	2			
14	8	2				
15	2	1				
Totals	921	319	50	352	43	2

the same as was earlier found with tablets containing norethindrone 2 mg and mestranol 0.1 mg.

A summary of co-operative clinical trials of norethindrone 1 mg combined with mestranol 0.05 mg described 3112 subjects who had used the drug for 20,692 cycles without any pregnancy (Syntex 1966). The frequency of break through bleeding and spotting, 21.8 per cent during the first cycle fell progressively to 4 per cent after the sixth.

Employing the same dosage, the frequency of break-through bleeding and spotting in this trial was 75 per cent initially and 22 per cent after six months of treatment. The latter percentage would have been still higher if not a considerable part of the patients with frequent break-through bleedings had been switched over to the tablets containing 0.1 mg estrogen. Amenorrhoea

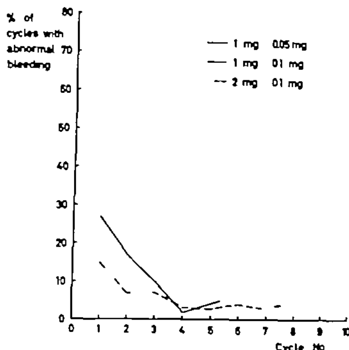


Fig. 1 Incidence of break through bleeding and spotting with 3 different norethindrone/mestranol combinations.

occurred in 5 4 per cent of the cycles The accuracy of the alleged constituents of the drugs used was tested and found satisfactory

Goldzieher and *Rice-Wray* (1966) pointed out that there is evidence to suggest that the dose of estrogen required to inhibit ovulation is not uniform for different populations. According to these authors *Liggins* (unpublished study) showed that a sequential regimen with 0 05 mg ethinyl estradiol gave a preg nancy rate of 14 9 per 100 women-years in New Zeeland. *Kaiser et al* (1966) obtained a pregnancy rate of 28 6 using 0 05 mg ethinyl estradiol sequentially in a group of Swedish women On the other hand, *Goldzieher* and *Rice-Wray* (1966) observed no pregnancy when they used the same dose of ethinyl estradiol for 20 days (with no gestagen at all) in a clinical trial in Mexico

Gross differences in nutrition heredity and environment may account for variations in the estrogen requirements of different populations However no quite satisfactory explanation can be offered for the variance in the results of this study and previous ones.

SUMMARY

Earlier studies have shown that a combination of norethindrone 1 mg and mestranol 0.05 mg is a good oral contraceptive agent. When used by a group of Swedish university students however it gave an intolerable high frequency of bleeding irregularities. When the estrogen dosage was increased to 0 mg the results were favourable.

REFERENCES

Goldzieher J W and *Rice-Wray E* "Oral Contraception p 85 Thomas Springfield, 1966

Kaiser I Wide L and *Gemzell C*, Acta Obst t Gynec. Scand. 45 53, 1966

Larsson-Cohn U Svenska Läkartidn. 61 1328, 1964

Syntex Research Data submitted to the U.S Federal Administration, 1966

Received on March 23rd, 1967

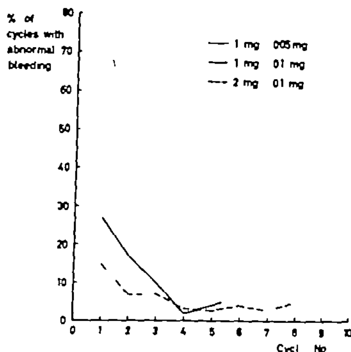


Fig. 1 Incidence of break-through bleeding and spotting with 3 different norethindrone/mestranol combinations

occurred in 5.4 per cent of the cycles. The accuracy of the alleged constituents of the drugs used was tested and found satisfactory.

Goldzieher and *Rice-Wray* (1966) pointed out that there is evidence to suggest that the dose of estrogen required to inhibit ovulation is not uniform for different populations. According to these authors *Liggins* (unpublished study) showed that a sequential regimen with 0.05 mg ethinyl estradiol gave a pregnancy rate of 14.9 per 100 women years in New Zeeland. *Kaiser et al.* (1966) obtained a pregnancy rate of 28.6 using 0.05 mg ethinyl estradiol sequentially in a group of Swedish women. On the other hand *Goldzieher* and *Rice-Wray* (1966) observed no pregnancy when they used the same dose of ethinyl estradiol for 20 days (with no gestagen at all) in a clinical trial in Mexico.

Gross differences in nutrition, heredity and environment may account for variations in the estrogen requirements of different populations. However, no quite satisfactory explanation can be offered for the variance in the results of this study and previous ones.

SUMMARY

Earlier studies have shown that a combination of norethindrone 1 mg and mestranol 0.05 mg is a good oral contraceptive agent. When used by a group of Swedish university students however it gave an intolerable high frequency of bleeding irregularities. When the estrogen dosage was increased to 0 mg, the results were favourable.

REFERENCES

Goldzieher J W and Rice-Wray E, "Oral Contraception" p. 65, Thomas, Springfield, 1966

Kaiser J Wide L and Gemzell C, Acta Obst et Gynec Scand 45 53 1966

Larsson-Cohn U Svenska Läkartidn 61 1328 1964

Syntex Research Data submitted to the U S Federal Administration, 1966

Received on March 23rd, 1967

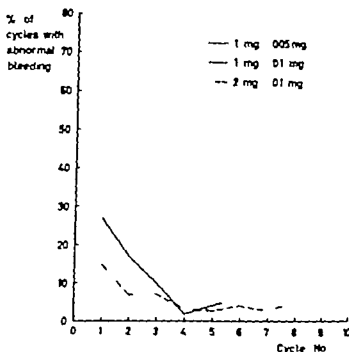


Fig. 1 Incidence of break-through bleeding and spotting with 3 different norethindrone mestranol combinations

occurred in 5 4 per cent of the cycles. The accuracy of the alleged constituents of the drugs used was tested and found satisfactory

Goldzieher and *Rice-Wray* (1966) pointed out that there is evidence to suggest that the dose of estrogen required to inhibit ovulation is not uniform for different populations. According to these authors *Liggins* (unpublished study) showed that a sequential regimen with 0 05 mg ethinyl estradiol gave a pregnancy rate of 14 9 per 100 women years in New Zeeland. *Kaiser et al* (1966) obtained a pregnancy rate of 28.6 using 0 05 mg ethinyl estradiol sequentially in a group of Swedish women. On the other hand, *Goldzieher* and *Rice-Wray* (1966) observed no pregnancy when they used the same dose of ethinyl estradiol for 20 days (with no gestagen at all) in a clinical trial in Mexico

Gross differences in nutrition, heredity and environment may account for variations in the estrogen requirements of different populations However no quite satisfactory explanation can be offered for the variance in the results of this study and previous ones

SUMMARY

Earlier studies have shown that a combination of norethindrone 1 mg and mestranol 0.05 mg is a good oral contraceptive agent. When used by a group of Swedish university students however it gave an intolerable high frequency of bleeding irregularities When the estrogen dosage was increased to 0 mg, the results were favourable

REFERENCES

Goldzieher J W and Rice-Wray E., "Oral Contraception p 85 Thomas, Springfield, 1966

Kaber I Wide L and Gemzell C., Acta Obst et Gynec. Scand 45 53, 1966

Larsson-Cohn *U* Svenska Läkartidn. *61* 1328 1964

Syntex Research Data submitted to the U.S Federal Administration, 1966

Received on March 23rd, 1967

Hilden, M. Amris, C. J. and Starup, J. Acta obst. et gynec. scandinav. 46, 562, 1967

From the Department of Clinical Chemistry Coagulation Laboratory (Professor P. Astrup) Rigshospitalet University of Copenhagen and the Department of Gynaecology and Obstetrics (E. Ostergaard M.D.) Frederiksberg Hospital Copenhagen Denmark

THE HAEMOSTATIC MECHANISM IN ORAL CONTRACEPTION

BY

M. HILDEN C. J. AMRIS AND J. STARUP

In 1963 *Egeberg* and *Owren* first demonstrated changes in coagulation in patients who were being treated with oral contraceptives. They found increased concentrations of factors VII and VIII and shortening of the cephalin time. Subsequently many reports have been published in which these findings were verified with some quantitative differences. In a previous study (*Amris* and *Starup* 1967) four patients were examined at intervals of 2 weeks for periods up to 16 months before during, and after cyclical treatment with Delpregnin® (each tablet contains 5 mg of megestrol acetate + 0.1 mg of mestranol). The study showed that factors II + VII (the Owren P and P test) and the plasminogen concentration were increased, and that the thromboplastin formation was accelerated immediately after the commencement of treatment, rose to a maximum during treatment and became normal again within the first 1 or 2 months after cessation of treatment. The concentration of factors VIII and V showed no permanent changes whereas factor VIII was at times greatly increased. Changes of the same nature were found in a group of normal pregnant women. The concentration of fibrinogen did not change during treatment with Delpregnin and no signs of inhibition of the fibrinolytic system could be demonstrated. In 2 patients the bleeding time was occasionally slightly prolonged.

The purpose of the present study was firstly to supplement the former investigation by elucidation of the thrombocyte function,

the vascular function, and the fibrinolytic system in patients during cyclical treatment with Delpregnin and secondly to compare these parameters and the coagulation status in pregnant and normal women, with those observed in Delpregnin-treated women.

Material and Methods

Three groups, each comprising 10 women, were studied

1) normal women who at the time of study had been treated cyclically with Delpregnin for periods ranging from 15 to 17 months,
2) normal, pregnant women in their 5th to 7th month of pregnancy
3) normal nulliparae.

All the patients were examined as out-patients. The tests were performed independent of the phase of the menstrual cycle. In none of the women studied had abnormal bleeding tendencies or thrombo-embolic disorders been diagnosed previously The average age appears from Table I.

Blood samples were taken a few hours after breakfast. The blood sampling technique and methods not described here, were as described in previous publications (*Amris* and *Kjeldsen* 1966 *Amris* and *Starup* 1967) *Plasminogen* was determined as described by *Alkjaersig, Fletcher* and *Sherry* (1959) *fibrinolytic activity* was determined on fibrin plates by the method of *Astrup* and *Müllertz* (1953) *Fibrinolysis inhibitors* against urokinase and plasmin were evaluated in the following way 0.25 ml of patient's plasma was added to 9 ml of fibrinogen 0.1 % and from this mixture a fibrin plate was produced, as described by *Astrup* and *Müllertz* (1953) Drops of 0.03 ml urokinase (UK) (Leo Pharmaceutical, Copenhagen) 4 units per ml, and plasmin (Lysofibrin® NOVO Industries, Copenhagen) 1.0 unit per ml, were placed on the plate. Following incubation at 37° for 20 hours, the areas of the zones of lysis appearing were read, and the reciprocal value of these areas was applied as an expression of the urokinase and plasmin inhibitors content

Hilden, M Amris, C. J and Starup J Acta obst et gynec. scandinav 46, 562, 1967
From the Department of Clinical Chemistry Coagulation Laboratory (Profe sor P Astrup) Rigshospitalet University of Copenhagen and the Departme of Gynaecology and Obstetrics (E. Østergaard M.D) Frederiksberg Hospit Copenhagen Denmark

THE HAEMOSTATIC MECHANISM IN ORAL CONTRACEPTION

BY

M. HILDEN, C. J AMRIS AND J STARUP

In 1963 *Egeberg* and *Owren* first demonstrated changes i coagulation in patients who were being treated with oral contra ceptives *They found increased concentrations of factors VII an* VIII and shortening of the cephalin time Subsequently man reports have been published in which these findings were verifie with some quantitative differences In a previous study (*Amri* and *Starup* 1967) four patients were examined at intervals o 2 weeks for periods up to 16 months before during, and afte cyclical treatment with Delpregnin[R] (each tablet contains 5 mg of megestrol acetate + 0 1 mg of mestranol) The study showed that factors II + VII (the Owren P and P test) and the plasm inogen concentration were increased, and that the thromboplastin formation was accelerated immediately after the commencement of treatment rose to a maximum during treatment and became normal again within the first 1 or 2 months after cessation of treatment The concentration of factors VIII and V showed no permanent changes whereas factor VIII was at times greatly increased. Changes of the same nature were found in a group of normal pregnant women The concentration of fibrinogen did not change during treatment with Delpregnin and no signs of inhibition of the fibrinolytic system could be demonstrated. In 2 patients the bleeding time was occasionally slightly prolonged.

The purpose of the present study was firstly to supplement the former investigation by elucidation of the thrombocyte function,

the vascular function, and the fibrinolytic system in patients during cyclical treatment with Delpregnin and secondly to compare these parameters and the coagulation status, in pregnant and normal women with those observed in Delpregnin-treated women.

Material and Methods

Three groups, each comprising 10 women, were studied

1) normal women who at the time of study had been treated cyclically with Delpregnin for periods ranging from 15 to 17 months,
2) normal, pregnant women in their 5th to 7th month of pregnancy
3) normal nulliparae.

All the patients were examined as out-patients. The tests were performed independent of the phase of the menstrual cycle. In none of the women studied had abnormal bleeding tendencies or thrombo-embolic disorders been diagnosed previously. The average age appears from Table I.

Blood samples were taken a few hours after breakfast. The blood sampling technique and methods not described here, were as described in previous publications (*Amris* and *Kjeldsen* 1966 *Amris* and *Starup* 1967) *Plasminogen* was determined as described by *Alkjaersig*, *Fletcher* and *Sherry* (1959) *fibrinolytic activity* was determined on fibrin plates by the method of *Astrup* and *Müllertz* (1953) *Fibrinolysis inhibitors* against urokinase and plasmin were evaluated in the following way 0.25 ml of patient's plasma was added to 9 ml of fibrinogen 0.1 % and from this mixture a fibrin plate was produced, as described by *Astrup* and *Müllertz* (1953) Drops of 0.03 ml urokinase (UK) (Leo Pharmaceutical Copenhagen) 4 units per ml, and plasmin (Lysofibrin® NOVO Industries Copenhagen) 1.0 unit per ml, were placed on the plate. Following incubation at 37° for 20 hours the areas of the zones of lysis appearing were read, and the reciprocal value of these areas was applied as an expression of the urokinase and plasmin inhibitors content

Table I. *Tests of the Vascular and Platelet Function in the 3 Groups of Patients Examined N = normal. The Values Are Average Values ± SD The Age of the Patients Is Given as Average Age Values in Brackets Indicate the Youngest and the Oldest Patient*

	Delpregnin Group	Pregnant Group	Control Group
Bleeding time sec. Duke	193 ± 35	179 ± 76	258 ± 34
Ivy	232 ± 63	261 ± 51	306 ± 93
Platelet concentration, × 10 /μl	206 ± 48	180 ± 46	220 ± 50
Platelet aggregation time			
sec. with ADP 0.3 μ/ml	8 ± 2	8 ± 2	7 ± 2
0.03 μ/ml	18 ± 5	13 ± 3	14 ± 3
Platelet adhesiveness %	61 ± 14	45 ± 19	47 ± 10
Platelet morphology			
(phase contrast microscopy)	N	N	N
Clot retraction	N	N	N
Prothrombin consumption test	N	N	N
Tourniquet test	N	N	N
Angiostereometry	N	N	N
Haemoglobin, g per 100 ml	12.9 ± 0.7	11.5 ± 1.0	12.4 ± 0.6
Age of patients	22.1 (18–27)	24.2 (17–31)	23.0 (20–26)

of the sample of plasma Factors VIII and IX were determined by using haemophilic plasma as substrate plasma in the following kaolin-cephalin-system 0.1 ml of substrate plasma + 0.1 ml of test plasma (strength 1/20–1/80) + 0.1 ml of a 2% kaolin suspension in Owren's buffer + 0.1 ml of cephalin from (human brain, optimum concentration) were preheated for 3 min. at 37 C The clotting time was determined after addition of 0.1 ml of calcium chloride 1/40 M The standard curve was prepared for each series of analyses by testing pooled plasma from 10 normal individuals The *capillary resistance* was determined by the tourniquet test (80 mm Hg/6 min) on the arm and in cases of negative pressure by means of angiosterometry as described by Parrot The *bleeding time* was determined by the method of Ivy (*Ivy Shapiro* and *Melnick* 1935) with the modification that instead of incisions three standardized punctures 4×2 mm, were made by means of a Sera Sharp[R] lancet (Propper Manu-

Table II. Determination of Clotting Factors in the 3 Groups of Patients Examined The Values Are Average Values ± SD

	Delpregnin Group	Pregnant Group	Control Group
Factors II VII	154 ± 17	147 ± 26	93 ± 9
Factor V	79 ± 15	115 ± 20	106 ± 20
Factor VIII	111 ± 30	153 ± 51	134 ± 40
Factor IX	119 ± 35	131 ± 55	85 ± 21

facturing Co., Inc.) The *platelet adhesiveness* in vitro was determined by the method of Hellem (1960) *Platelet aggregation* with A.D.P. (adenosine diphosphate) was determined in platelet rich plasma at room temperature, 0.5 ml of plasma + 0.05 ml of A.D.P. (3.0 and 0.3 μg/ml in Owren's buffer) in tubes, 80 × 9 to 10 mm. After addition of A.D.P. the tube was rotated at an angle of 15° to the horizontal plane, and the period of time required for the formation of visible aggregates read. Mean values of duplicate determinations were calculated. The *clot retraction* was determined in platelet-rich plasma following coagulation with thrombin, 0.5 ml of plasma + 0.05 ml of thrombin, 10 units per ml, at 37° for 1 hour. The result was evaluated qualitatively by comparing with a normal control sample. The *platelet morphology* was evaluated by means of phase contrast microscopy of platelet-rich plasma during and after coagulation by addition of calcium chloride.

Average values for the 3 groups examined were compared on the basis of the t-test with SD estimated from the 3 groups collectively (27 degrees of freedom). In cases where the results of the analyses made it reasonable, logarithmic transformation was applied. The variation of significance at the 5 % level is termed (level of significance 5 %) and the same applies to the 1 % and the 0.1 % levels.

Results

The results of the platelet and capillary function tests appear in Table I. The groups are not significantly different.

Table I Tests of the Vascular and Platelet Function in the 3 Groups of Patients Examined. N = normal. The Values Are Average Values ± SD The Age of the Patients is Given as Average Age Values in Brackets Indicate the Youngest and the Oldest Patient

	Delpregnin Group	Pregnant Group	Control Group
Bleeding time sec. Duke	193 ± 35	179 ± 76	258 ± 34
Ivy	23? ± 63	261 ± 51	306 ± 93
Platelet concentration, × 10 /μl	206 ± 48	180 ± 46	220 ± 50
Platelet aggregation time			
sec. with A.D.P 0.3 μ/ml	8 ± 2	8 ± 2	± 2
0 03 μ/ml	18 ± 5	13 ± 3	14 ± 3
Platelet adhesiveness %	61 ± 14	45 ± 19	47 ± 10
Platelet morphology			
(phase contrast microscopy)	N	N	N
Clot retraction	N	N	N
Prothrombin consumption test	N	N	N
Tourniquet test	N	N	N
Angiostereometry	N	N	N
Haemoglobin, g per 100 ml	12 9 ± 0 7	11.5 ± 1 0	12.4 ± 0 6
Age of patients	22 1 (18–27)	24 2 (17–31)	23 0 (20–26)

of the sample of plasma Factors VIII and IX were determined by using haemophilic plasma as substrate plasma in the following kaolin-cephalin-system 0 1 ml of substrate plasma + 0 1 ml of test plasma (strength 1/20–1/80) + 0 1 ml of a 2 % kaolin suspension in Owren s buffer + 0 1 ml of cephalin from (human brain optimum concentration) were preheated for 3 min. at 37 C The clotting time was determined after addition of 0 1 ml of calcium chloride 1/40 M. The standard curve was prepared for each series of analyses by testing pooled plasma from 10 normal individuals The *capillary resistance* was determined by the tourniquet test (80 mm Hg/6 min) on the arm and in cases of negative pressure by means of angiosterometry as described by Parrot The *bleeding time* was determined by the method of Ivy (*Ivy Shapiro* and *Melnick* 1935) with the modification that instead of incisions three standardized punctures 4 × 2 mm, were made by means of a Sera Sharp® lancet (Propper Manu-

Table III. *Tests of the Fibrinolytic System in the 3 Groups of Patients Examined. The Values Are Average Values ± SD*

	Delpregnin Group	Pregnant Group	Control Group
Fibrinogen, g per 100 ml	0.32 ± 0.03	0.35 ± 0.04	0.27 ± 0.04
Plasma thrombin time sec.	11.1 ± 1.3	10.3 ± 1.1	10.3 ± 0.8
Activity on fibrin plates, sq mm.			
plasma	5 17 ± 18		
	5 0	0	0
euglobulin	109 ± 53	15 ± 14	60 ± 27
Euglobulin clot lysis time, min.	190 ± 51	10 > 300	5 > 300
			5 191 ± 31
Inhibitor (fibrin plate method) against			
urokinase, sq mm.	138 ± 24	91 ± 13	141 ± 8
plasmin, sq mm.	169 ± 18	157 ± 18	202 ± 17
Plasminogen, %	172 ± 15	144 ± 19	102 ± 15

than that in the normal group (level of significance 1 %). The urokinase inhibitor in the pregnant group is higher than that in normal women and in the Delpregnin-group (the level of significance in either case 5 %). The euglobulin activity on fibrin plates among the pregnant women is lower than that in normal women and in the Delpregnin-group (level of significance in either group 0.1 %). A similar tendency is seen for the euglobulin clot lysis time. As regards the remaining parameters in Table III the groups show no significant differences.

Discussion

In our previous investigation (Amris and Starup 1967) it was shown that the alterations in the coagulation, during treatment with Delpregnin, quickly reached a plateau which did not change during continued treatment, and no cyclic variations were found. By studying normal women, *Brakman et al.* (1966) were not able to reveal significant alterations in the coagulation and fibrinolysis related to menstruation. Therefore, we are of the opinion that our 3 groups are comparable, even if the examinations were carried out irrespective of the patients cycle.

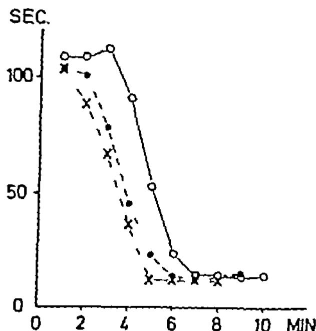


Fig. 1 Calculated mean curves for the thromboplastin screening test in the 3 groups of patients examined.
Abscissa. time of incubation in minutes.
Ordinate substrate plasma clotting time in seconds.

o——o control group
●- - - -● Delpregnin-group
X- - -X pregnant group

In Table II the coagulation tests are presented collectively It will be seen that factors II + VII (the Owren P & P test) are increased significantly in the Delpregnin-group and in the pregnant women as compared with the control group (level of significance in either case 0 1 %) Factors V VIII and IX do not present any significant differences in the 3 groups.

Fig 1 shows the calculated average curves for the thromboplastin screening tests in the groups It will be seen that the curves representing the Delpregnin-group and the pregnant group are steeper and have lower minima than the curve representing the controls, indicating an acceleration of the formation of thromboplastin in the first 2 groups

In Table III the fibrinolytic determinations are listed. The plasminogen concentration in the Delpregnin-group is higher

Table III. Tests of the Fibrinolytic System in the 3 Groups of Patients Examined. The Values Are Average Values ± SD

	Delpregnin Group	Pregnant Group	Control Group
Fibrinogen, g per 100 ml	0.32 ± 0.03	0.35 ± 0.04	0.27 ± 0.04
Plasma thrombin time, sec.	11.1 ± 1.3	10.3 ± 1.1	10.3 ± 0.8
Activity on fibrin plates, sq mm			
plasma	5 17 ± 18		
	3 0	0	0
euglobulin	109 ± 53	15 ± 14	69 ± 27
Euglobulin clot lysis time, min.	190 ± 51	10 > 300	5 > 300
			5 191 ± 31
Inhibitor (fibrin plate method) against			
urokinase, sq mm.	138 ± 24	91 ± 13	141 ± 8
plasmin, sq mm	169 ± 18	157 ± 18	202 ± 17
Plasminogen, %	172 ± 15	144 ± 19	102 ± 15

than that in the normal group (level of significance 1 %). The urokinase inhibitor in the pregnant group is higher than that in normal women and in the Delpregnin-group (the level of significance in either case 5 %). The euglobulin activity on fibrin plates among the pregnant women is lower than that in normal women and in the Delpregnin-group (level of significance in either group 0.1 %). A similar tendency is seen for the euglobulin clot lysis time. As regards the remaining parameters in Table III the groups show no significant differences.

Discussion

In our previous investigation (*Amris* and *Starup* 1967) it was shown that the alterations in the coagulation, during treatment with Delpregnin, quickly reached a plateau which did not change during continued treatment, and no cyclic variations were found. By studying normal women, *Brakman et al.* (1966) were not able to reveal significant alterations in the coagulation and fibrinolysis related to menstruation. Therefore, we are of the opinion that our 3 groups are comparable, even if the examinations were carried out irrespective of the patients cycle.

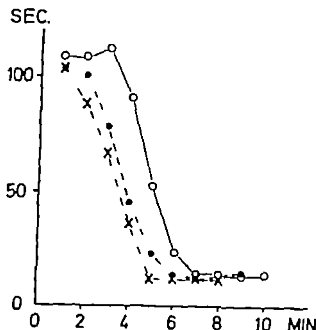


Fig. 1 Calculated mean curves for the thromboplastin screening test in the 3 groups of patients examined.
Abscissa time of incubation in minutes.
Ordinate substrate plasma clotting time in seconds.

o——o control group
●----● Delpregnin-group
X- - -X pregnant group

In Table II the coagulation tests are presented collectively It will be seen that factors II + VII (the Owren P & P test) are increased significantly in the Delpregnin-group and in the pregnant women as compared with the control group (level of significance in either case 0 1 %) Factors V VIII and IX do not present any significant differences in the 3 groups

Fig 1 shows the calculated average curves for the thromboplastin screening tests in the groups. It will be seen that the curves representing the Delpregnin-group and the pregnant group are steeper and have lower minima than the curve representing the controls, indicating an acceleration of the formation of thromboplastin in the first 2 groups.

In Table III the fibrinolytic determinations are listed. The plasminogen concentration in the Delpregnin-group is higher

(1965) During anovulatory treatment diverse findings have been reported. An increase as demonstrated by the present authors, was reported by *Phillips et al* (1961) *Brehm* (1964) and others whereas *Brakman* and *Astrup* (1964) found unchanged concentration of plasminogen during the anovulatory treatment. Reports concerning the concentration of fibrinogen show similar variations. Some authors (*e.g. Brakman* and *Astrup* 1964 *Ammundsen* and *Pilgeram* 1964 *Müller et al* 1965 *Donayre* and *Pincus* 1965) found increased values whereas others found the concentration to be constant (*Margulis et al* 1965 *Powell et al* 1965) The diverse results may be explained by differences in the methods applied, or rather the use of various hormonal drugs and dosage of such drugs.

Many investigators presume that fibrin formation and fibrinolysis normally are in a delicate dynamic balance, so that constant intravascular fibrin formation is kept in equilibrium with perfectly adapted fibrinolysis. Changes in this equilibrium towards increased coagulation and/or reduced fibrinolysis should increase the risk of thrombosis.

If the changes observed in coagulation and fibrinolysis in the 3 groups of patients are viewed in relation to this theory of equilibrium, the Delpregnin-treated group must be supposed to present a lesser risk of thrombosis than the pregnant group. Alterations towards "hypercoagulability" are identical in the two groups but, contrary to the pregnant women, the Delpregnin-treated women present a significantly increased fibrinolysis and no increase in the fibrinolytic inhibitors.

During recent years, attention has been directed towards an increased platelet adhesiveness, indicating a tendency to thrombosis. As already mentioned, we found no significant difference between the groups in this respect even if we found a tendency to slightly increased adhesiveness in the Delpregnin-group. However the circumstances relating thereto are still obscure. No experimental support for a definite relationship between thrombotic diseases and increased platelet adhesiveness has yet been found. Also the theory of equilibrium is not clearly substantiated by experiments and consequently we have no laboratory parameters which can disclose with certainty a latent risk of throm-

The analytical technique applied did not reveal any changes in the vascular or platelet function in the Delpregnin treated women. Thus it was not possible to reproduce the slight and transient prolongation of the bleeding time during treatment with Delpregnin which has previously been observed (*Amris* and *Starup* 1967). Therefore we find no grounds for supposing that Delpregnin produces any changes in the haemostatic function. In 1965, *Caspary* and *Peberdy* reported that the adhesiveness of platelets to glass surfaces in vitro was increased during treatment with Conovid[R] and Anovlar[R]. We found no significant increase during treatment with Delpregnin, although we observed a tendency to increased adhesiveness.

The changes observed in the coagulation system in pregnant and Delpregnin treated women, the significant increase in factors II + VII and the acceleration of the formation of thromboplastin, agree with previous findings (*Amris* and *Starup* 1967). During the previous investigation a transient increase in factor VIII was found. This variability was supposed to be caused by a possible effect of accelerators of coagulation in the test system applied, *e.g.* in the form of an incontrollable contact activation. Therefore in the present study we used a test system in which we aimed at a maximum and controllable contact activation of the measuring system by adding kaolin. When employing this technique we did not find a variability in factor VIII similar to that previously observed. This supports the assumption that the former variation in factor VIII should be interpreted as being caused by the applied technique rather than a genuine increase in the factor concerned.

The urokinase inhibitor in the pregnant group was found to be significantly higher than that found in the other two groups. This is in agreement with the findings of *Brackman* and *Astrup* (1964). Correspondingly reduced fibrinolytic activity was found in our group of pregnant women. This is a well known phenomenon (see inter alia *Sharper et al.* 1966). In 1964 *Brackman* and *Astrup* reported that the urokinase inhibitor did not change during oral contraception and this finding was confirmed by our investigation. Increased concentration of plasminogen during pregnancy has been described inter alia by *Hedner* and *Nilsson*

creased risk of thrombosis is discussed. It is concluded that it is not possible at present to assess the risk of thrombo-embolic complications during oral contraception on the basis of the laboratory parameters available. This problem can be clarified only by means of more comprehensive clinical studies covering a sufficiently large number of controls.

Acknowledgement

We thank Jørgen Hilden, M.D. University Institute of Medical Genetics, Copenhagen for help and valuable advice to the statistical calculations.

REFERENCES

Alkjaersig, N. Fletcher A. P. and Sherry S. J. clin. Invest. 38 1086, 1959
Amris, C. J. and Kjeldsen J. Acta obst. et gynec. scandinav. 45 180, 1966
Amris, C. J. and Starup J. Acta obst. et gynec. scandinav. 46 78 1967
Amundson B. A. and Pilgeram L. O. Thromb. Diath. Haemorrh. X 400 1964
Astrup T. and Müllertz S. Arch. Biochem. Biophys. 40 346, 1952
Brakman P. and Astrup T. Scand. J. clin. Lab. Invest. 15 603 1963
Lancet, II 10, 1964
Brakman P. Albrechtsen O. K. and Astrup T. Brit. J. Haemat. 12 4 1966
Brehm, H. Int. J. Fertil. 9 45 1964
Caspary E. A. and Peberdy Mary Lancet I 1142, 1965
Dowsyne J. and Pracies C. Metabolism 14 418, 1965
Egeberg, O. and Owren P. A. Brit. med. J. I 220 1963
Hedner U. and Nilsson I. M. Thromb. Diath. Haemorrh. (Stuttg.) 14 545, 1965
Hellem, A. J. Scand. J. clin. Lab. Invest. Suppl. 12, 1960
Fry A. C. Shapiro P. R. and Melnick P. Surg. Gynec. & Obstet. 60 781 1935
Margulis R. R. Ambrus J. L. Mink I. B. and Stryker J. C. Amer. J. Obstet. Gynec. 93 161 1965
Miller S. P. Lee S. L. and Ritz N. Metabolism 14 398, 1965
Perrot J. L. G. R. Soc. Biol. Paris, 147 1946 1953
Phillips L. L. Turksoy R. N. and Southam A. L. Amer. J. Obstet. Gynec. 82 1216, 1961
Powell, L. C. Gurest M. M. and Bond T. P. Amer. J. Obstet. Gynec. 93 167 1965
Shaper A. G. Macintosh D. M. and Kyobe J. Lancet II 874, 1966

Received on Feb. 15th, 1967

bosis. The problem as to whether oral contraception will increase the risk of thrombo-embolic disorders must be finally solved by well-controlled clinical investigations.

SUMMARY

Three groups of women of identical age were investigated

1) 10 normal women treated cyclically with Delpregnin® (5 mg of megestrol acetate + 0.1 mg of mestranol) for periods ranging from 15 to 17 months
2) 10 normal pregnant women in their 5th to 7th month of pregnancy
3) a control group comprising 10 normal nulliparae.

They were examined by means of a number of analysis for the purpose of elucidating the platelet and vascular function, as well as the mechanism of coagulation and fibrinolysis. Treatment with Delpregnin produced no changes in the haemostatic function, which we attempted to clarify by determining the bleeding time, the capillary resistance platelet count, platelet adhesiveness, platelet aggregation with A.D.P. platelet morphology clot retraction and prothrombin consumption. Factors II + VII (the Owren P & P test) were found to be significantly increased in the Delpregnin treated and the pregnant groups as compared with the controls. No significant differences in factors V VIII and IX were found between the 3 groups but the thromboplastin formation was found to be slightly accelerated in the Delpregnin group and in the pregnant women. By fibrinolytic determinations, the following differences were found between the 3 groups: plasminogen was increased significantly in the Delpregnin-treated group and in the pregnant women, the fibrinolytic activity was reduced in the pregnant group unchanged or slightly increased in the Delpregnin-treated group as compared with the controls. Urokinase inhibitor was significantly increased in the pregnant group but unchanged as compared with the controls, in the Delpregnin-treated group. No significant differences were found in respect of fibrinogen, plasmin inhibitor and antithrombin.

The relationship between the changes observed and an in-

a significant effect on menorrhagia (*Nilsson L.* and *Rybo* 1966). The mode of action of AMCA is the same as that of EACA, involving primarily the inhibition of the plasminogen activation (*Okamoto S* and *Okamoto U* 1962, *Oshiba* and *Okamoto S* 1962, *Dubber McNichol Douglas* and *Melander* 1964, *Dubber McNichol*, and *Douglas* 1965, *Melander Gliniecki Granstrand* and *Hanshoff* 1965, *Andersson Nilsson I M. Nilehn Hedner Granstrand* and *Melander* 1965).

The aim of the present work was to investigate by double blind trial and dose-response studies the effect of AMCA on the menstrual blood loss, and to determine the appropriate dosage.

Material and Methods

The series consisted of 36 women between the ages of 15 and 49 (mean age 38) who were referred to the Department on account of suspected menorrhagia. A general gynaecological examination was made at the first visit. To ascertain that the bleeding was ovulatory premenstrual curettage was performed in 22 women, all of these had secretory endometrium. In the remaining 15 patients curettage has not yet been performed. Five of the women were subjected to hysterosalpingography.

Fibroids were demonstrated in 3 patients, and suspected in 2 more. Subsequent hysterectomy in one woman revealed adenomyosis.

In all the women taking part in the trial, blood loss was measured during 5 consecutive menstrual cycles. During 2 of these cycles no medication was given. In the other 3 cycles each patient received a preparation marked respectively I, II and III for the first, second, and third of these cycles. One of the preparations contained a placebo, and the other 2 contained AMCA (Cyklokapron preparation supplied by AB Kabi, Stockholm). One of the AMCA preparations contained 0.25 g of the active substance per tablet and the other 0.5 grams. Thus, each patient received tablets containing placebo, 0.25 g, and 0.5 g of AMCA allocated to random distribution as in a double blind trial. In the initial stages of the trial the dosage was 1 tablet 6 times daily during the first four days of the period, corresponding to a total

Nilsson, Lennart and Rybo, Göran, Acta obst. et gynec. scandinav. 46, 572, 1967
From the Department of Obstetrics and Gynaecology (Professor Sam Brody)
University of Göteborg, Sweden

TREATMENT OF MENORRHAGIA WITH AN ANTIFIBRINOLYTIC AGENT TRANEXAMIC ACID (AMCA)

A Double Blind Investigation

BY

LENNART NILSSON AND GÖRAN RYBO

Iron deficiency is a common disorder among women of childbearing age (*Hallberg*, 1964 *Jacobs Kilpatrick* and *Withey*, 1965) This may be caused by defective dietary intake of iron, an increased need of iron in pregnancy or an increased loss of iron due to various forms of bleeding Menorrhagia, an example of the latter group of factors is a common cause of iron deficiency Thus it was found in a population study that 66 per cent of the women whose menstrual blood loss exceeded 80 ml per period, suffered from anaemia (haemoglobin concentration below 12 g per 100 ml blood) and of those women whose loss of blood exceeded 60 ml, 54 per cent had anaemia (*Hallberg, Högdahl Nilsson L* and *Rybo* unpublished) Therefore menorrhagia should always be considered in the diagnosis of iron deficiency in women of childbearing age

Fibrinolytic inhibitors such as epsilon-aminocaproic acid (EACA) have proved to be of value in the treatment of menorrhagia (*Nilsson I M Björkman* and *Andersson* 1961 *Nilsson, L , Rybo* and *Hallberg*, 1964 *Nilsson L* 1964 *Gennser* 1964 *Nilsson L* and *Rybo* 1965 *Nilsson I M* and *Björkman* 1965 *Nilsson L* and *Rybo* 1966) Another synthetic amino acid with a powerful fibrinolytic-inhibitory effect which has received attention during recent years is tranexamic acid (AMCA) In preliminary investigations this substance has been found to have

Table I. Blood Loss (ml) During Various Periods for Each Patient in the Series

Patient Number	Controls			Placebo	AMCA		Remarks
	I	II	Mean value		high dosage	low dosage	
1	107.2	89.5	98.4	66.4	48.2	34.6	
2	93.2	83.4	88.3	152.4	61.3	96.3	
3	88.8	81.2	85.5	70.0	45.2	66.0	
4	349.1	176.4	262.8	329.0	218.2	177.5	Subsequent hysterectomy Diagnosis adenomyosis.
5	143.5	127.5	135.5	149.4	98.2	102.9	
6	88.4	149.8	119.1	83.6	29.2	64.4	
7	115.9	74.7	95.3	97.0	30.1	82.2	Fibroids?
8	78.0	58.6	68.3	59.8	42.7	51.8	
9	133.7	91.9	112.8	74.9	78.7	58.1	
10	157.5	210.4	184.0	192.0	156.2	131.0	
11	168.0	172.7	170.4	163.9	59.2	93.0	Fibroids
12	156.1	280.8	218.5	163.5	79.6	62.1	
13	187.1	123.0	155.1	110.5		64.3	
14	205.1	236.1	220.6	185.3	69.6	106.4	
15	113.9	81.2	97.6	113.3	88.2	80.0	
16	63.1	78.3	70.7	85.1	21.6	33.6	
17	138.7	88.9	112.8	112.0	40.0	73.9	
18	77.4	102.9	90.2	68.0	48.7	46.2	
19	106.8	136.7	121.8	171.4	98.5	121.6	
20	130.7	69.2	100.0	52.7	52.1	30.4	
21	89.0	102.2	95.6	81.1	29.3	35.6	
22	247.2	157.2	202.2	119.3	50.0	104.0	
23	121.7	143.4	132.6	83.9	57.5	112.8	
24	56.7	36.3	46.5	42.6	34.8	36.2	
25	134.1	131.1	132.6	59.6	43.4	84.3	
26	101.0	88.2	94.6	44.0	27.9	51.1	
27	105.4	112.1	108.8	115.7	78.5	63.5	
28	96.0	77.2	86.6	94.8	40.0	41.7	
29	47.6	84.7	66.2	42.9	27.2	43.9	
30	241.9	434.4	338.2	246.0	87.7	261.4	
31	74.9	49.8	62.4	59.1	44.4	53.3	
32	136.0	123.1	129.6	139.8	80.2	70.9	
33	128.0	132.5	130.3	143.8	48.1	77.0	
34	264.6	229.7	247.2	260.7	145.4	250.6	Fibroids
35	87.5	93.1	90.3	48.1	27.9	126.4	Fibroids
36	218.7	326.8	272.8	261.7	297.3	162.7	Fibroids

dose of 6 and 12 grams of AMCA respectively, when the active drug was administered. When the first 8 patients participating in the trial had been treated the results for patients who did not belong to the present series indicated that, at any rate, the dosage of 6 grams was too low Consequently the dose was increased to 2 tablets 6 times daily for 4 days starting from patient no 9 This amounted to a total dose of either 12 or 24 grams of AMCA. Because of this change in the dosage statistical analysis was made both for the entire series including the first 8 patients and also for that part of the series in which the lower and the higher dosages of AMCA amounted to 12 and 24 grams respectively Some slight deviations from the prescribed dosage occurred. The menstrual blood loss was determined according to the method of *Hallberg* and *Nilsson L* (1964)

Results

Table I shows the blood loss during each period for all patients. Table II shows the mean blood loss for all patients during the periods when treatment was not given (controls) and during treatment with placebo and with AMCA respectively From these data it appears that the blood loss was reduced when AMCA was administered. The decrease in blood loss during AMCA treatment was statistically significant (Table III) On the other hand when the placebo was administered the reduction of the blood loss in relation to the control cycles was not statistically significant With regard to the effect of AMCA treatment no difference was observed between the women with and those without fibroids.

Variations in the amount of AMCA which different subjects received depended partly on the fact that the prescribed dosage was changed during the course of the trials and partly on the failure of some of the patients to follow the given dosage In order to study to what extent the reduction in blood loss, which was obtained when the patients were treated with AMCA was due to the size of the dose 19 women were selected each of whom received a total of 11–12 grams of AMCA in the low dosage, and a total of 23–24 grams in the high dosage Table IV

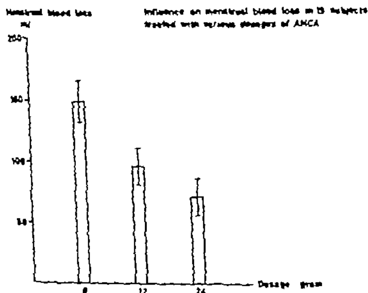


Fig 1

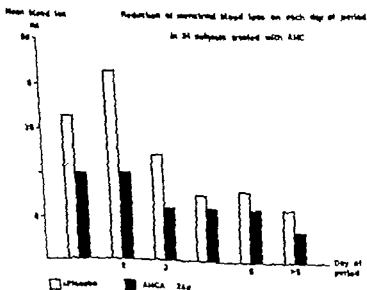


Fig 2.

Table II. *Mean Blood Loss (ml) During Various Periods*

	Controls		Mean value	Placebo	AMCA	
	1st period X_1	2nd period X_2		Z	high dosage Y_1	low dosage Y_2
Blood loss (mean value ± S.E. of mean)	134.8 ± 10.9	134.3 ± 13.7	134.5 ± 11.3	123.4 ± 12.9	70.9 ± 9.6	87.6 ± 9[illegible]

Table III. *Statistical Analyses*

Difference	Mean value	t-value	P
$L_1 = (X_1 - X_2) - (Z - Y_1)$	−54.3	−3.99	$p < 0.001$
$L_2 = (X_1 - X_2) - (Z - Y_2)$	−35.3	−3.0[illegible]	$p < 0.05$
$L_3 = (X_1 - X_2)$	0.46	0.04	$p > 0.10$
$L_4 = \frac{(X_1 + X_2)}{2} - Z$	11.1	1.[illegible]2	$0.05 < p < 0.10$

It is evident that L_1 and L_2 differ significantly from zero. As L_3 and L_4 do not differ from zero the observed differences must be due to Y_1 and Y_2.

Table IV. *Dose—Response of AMCA. (19 Subjects)*

Dosage (g)	Blood loss Mean value ± S.E. of mean	Reduction in per cent of controls
0	149.1 ± 1[illegible]	
12	96.1 ± 15	38 ± 4.47
24	71.0 ± 14.6	51 ± 5.23

and Fig. 1 show that there is a significant difference in the effects of these two dosages. When the dose was 12 grams (3 grams for 4 days) the mean reduction was 38 per cent, and when it was 24 grams (6 grams for 4 days) the corresponding figure was 51 per cent. Reduction per cent is based on the mean of the individual percentage reductions.

Fig. 2 shows the daily blood loss during the period for the 24

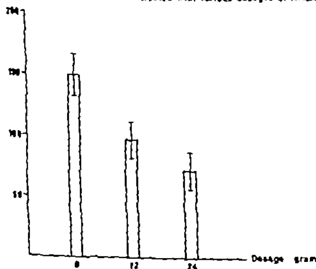

Dosage gram
0
12
24

Fig. 1

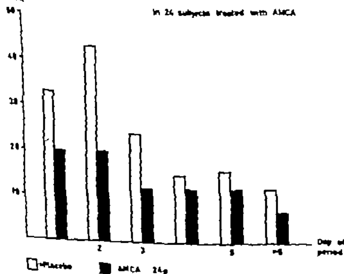

in 24 subjects treated with AMCA
2
3
5
Day of
period
Placebo
AMCA 24 g

Fig. 2.

Table II. *Mean Blood Loss (ml) During Various Periods*

	Controls		Mean value	Placebo	AMCA	
	1st period X_1	2nd period X_2		Z	high dosage Y_1	low dosage Y_2
Blood loss (mean value ± S.E. of mean)	134.8 ± 10.9	134.3 ± 13.7	134.5 ± 11.3	123.4 ± 12.9	70.9 ± 9.6	87.6 ± 9.2

Table III. *Statistical Analyses*

Difference	Mean value	t-value	P
$L_1 = (X_1 - X_2) - (Z - Y_1)$	−54.3	−3.99	$p < 0.001$
$L_2 = (X_1 - X_2) - (Z - Y_2)$	−35.3	−3.02	$p < 0.005$
$L_3 = (X_1 - X_2)$	0.46	0.04	$p > 0.10$
$L_4 = \frac{(X_1 + X_2)}{2} - Z$	11.1	1.72	$0.05 < p < 0.10$

It is evident that L_1 and L_2 differ significantly from zero. As L_3 and L_4 do not differ from zero, the observed differences must be due to Y_1 and Y_2.

Table IV *Dose—Response of AMCA. (19 Subjects)*

Dosage (g)	Blood loss Mean value ± S.E. of mean	Reduction in per cent of controls
0	149.1 ± 17.1	
12	96.1 ± 15.2	38 ± 4.47
24	71.0 ± 14.6	51 ± 5.23

and Fig 1 show that there is a significant difference in the effects of these two dosages When the dose was 12 grams (3 grams for 4 days) the mean reduction was 38 per cent and when it was 24 grams (6 grams for 4 days) the corresponding figure was 51 per cent Reduction per cent is based on the mean of the individual percentage reductions

Fig 2 shows the daily blood loss during the period for the 24

Discussion

From a methodological point of view the present investigation is based on four conditions designed to establish that the effect obtained is an expression of the pharmacological properties of the substance namely objective measurement of the effect, patients acting as their own controls double blind investigation, and dose-response study

The results clearly show that AMCA produces a significant decrease in menstrual blood loss in women suffering from menorrhagia. There was also some reduction of the blood loss when placebo was administered, but this was not statistically significant

In a previous investigation (*Nilsson L* and *Rybo* 1965) the effect of epsilon aminocaproic acid (EACA) on menorrhagia was studied, using the same experimental design as that applied in the present scheme With EACA a mean reduction of 60 per cent was obtained as against 50 per cent shown with AMCA. The difference may be due to the fact that EACA was given during the entire period, whereas AMCA was administered only during the first four days of the period. Also the dosages are not exactly comparable. In an investigation of a larger series (*Nilsson L* and *Rybo* 1966) where, however double blind technique was not applied and where the dosage varied, the mean reduction in blood loss obtained with EACA amounted to 50 per cent.

The substantial advantage in using AMCA is that the side effects occur less frequently and are less pronounced than when EACA is used This is demonstrated by the fact that only 8 patients had slight abdominal discomfort during AMCA treatment. The troublesome orthostatic reactions sometimes seen during EACA treatment were not observed with AMCA

When the total dosage of AMCA was 24 grams the reduction in the menstrual blood loss was greater than with a total dosage of 12 grams. A dosage of about 6 grams of AMCA daily seems to be adequate In some cases, however treatment for only four days may be regarded as too short, since here the blood loss was relatively high even during the ensuing days of the period.

Table V *Side Effects During Treatment with AMCA and with Placebo*

Patient number	AMCA high dosage	AMCA low dosage	Placebo
6	Dizziness	Headache nausea	Headache
9	–	–	Drowsiness
10	Slight diarrhoea	–	–
11	–	Slight nausea	Slight nausea
12	Abdominal pain	–	–
14	Slight diarrhoea	–	Nausea
20	Exanthema	–	–
22	Diarrhoea	–	–
23	Meteorism	–	–
24	Diarrhoea	–	–
25	Diarrhoea	Urgency	Heartburn
26	Diarrhoea	–	Headache
27	–	Abdominal pain	–
28	Abdominal pain	Abdominal pain nausea	–
29	–	Abdominal pain	–
30	Abdominal pain	–	–
31	Vomiting	–	Abdominal pain
32	–	Abdominal pain	–
35	–	–	Nausea

women who received a total dose of 24 grams of AMCA. It is evident that the effect was most pronounced during the first three days of the period

Side effects These are shown in Table V In 17 of the subjects there were no side effects related to either the AMCA treatment or the placebo. Two patients had side effects only when they received the placebo and 6 on the administration of both AMCA and the placebo In three patients side effects developed in connection with the low but not with the high dosage of AMCA. One subject had side effect with both the low and the high dosage. In 7 patients side effects occurred only with the high dosage of AMCA The main symptoms were stated to be diarrhoea and abdominal pains. In no case did treatment have to be discontinued on account of side effects.

Forsberg, John-Gunnar and Ingemanson, Carl-Axel, Acta obst. et gynec. scandinav. 46, 581 1967

From the Department of Anatomy and the Tornblad Institute for Comparative Embryology (Prof Bengt Källén) and the Department of Obstetrics and Gynaecology (Prof A. Sjövall) University of Lund, Sweden

SUCCESSFUL GROWTH OF HUMAN COLUMNAR CERVICAL EPITHELIUM GRAFTED INTO NEONATAL RATS

BY

JOHN-GUNNAR FORSBERG AND CARL AXEL INGEMANSON

Several studies have been devoted to the tissue culture of normal cervical epithelium (*e.g.* *Mellgren et al.* 1962 *Richart* 1964 a, 1964 b *Richart* and *Lerch* 1966 *Auersperg* and *Worth* 1966) In these cell culture studies interest has been mainly focused on the growth behaviour and characteristics of the epithelium and on this compared with that of abnormal cervical epithelium. The same object has been pursued also when normal portio epithelium has been cultured in the cheek-pouch of cortisone treated hamsters (*Mellgren et al.* 1962) Other studies have been devoted to analyses of the thymidine-H^3 cytidine-H^3 leucine-H^3 and cystine-S^{35} uptake in short-term incubations of cervical epithelium (*Reid* 1964 a *Fettig et al.* 1964 a, 1964 b 1966) and the sperm penetration through columnar and metaplastic epithelium in *in vitro* cultures for 15–24 hours (*Reid* 1964 b) Biochemical studies have been carried out on normal cervical tissue cultured for 72 hours in a synthetic medium (*Mainigi et al* 1965) No histological studies were made to establish the appearance of the tissue after the culture period.

It has not been possible to find any report in the literature on organ culture of human columnar cervical epithelium with a definite preservation of histological structure for a longer period than 24 hours.

In the course of an investigation on different aspects of metaplastic changes in the human uterine cervix, we wanted a

SUMMARY

The effect of tranexamic acid—AMCA—on the menstrual blood loss was studied in 36 women suffering from menorrhagia, by using a double blind and dose-response technique. The blood loss was estimated objectively. During the AMCA treatment there was a significant reduction in the blood loss amounting to about 50 per cent of that in the control cycles. The reduction was most marked during the first three days of the period, and increased with increasing dosage. Side effects were slight and did not necessitate discontinuing treatment.

REFERENCES

Andersson L. Nilsson I M Nilehn J E Hedner U Granstrand B and *Melander B.* Scand. J Haemat. 2 230 1965

Dubber A. H C Mc Nicol G P Douglas A. S and *Melander B.* Lancet 2 1317 1964

Dubber A. H C., McNicol G P and *Douglas A. S.* Brit. J Haemat. 11 237 1965

Gennser G Nord. Med. 71 778, 1964

Hallberg, L. and *Nilsson L.* Scand J Clin. Lab. Invest. 16 244 1964

Hallberg, L. Näringsforskning 8 1 1964

Jacobs A. Kilpatrick G S and *Whithey J L* Postgrad. Med. J 41 418, 1965

Melander B. Gliniecki G. Granstrand B and *Hanshoff G* Acta Pharmacol. et Toxicol. 22 340 1965

Nilsson I M Björkman S. E. and *Andersson L* Acta Med. Scand. 170 487 1961

Nilsson I M and *Björkman S E.* Acta Med. Scand 177 445, 1965

Nilsson L. Nord. Med. 71 777 1964

Nilsson L. Rybo G and *Hallberg, L* IVth World Congress of Gynecology and Obstetrics, 152, 1964

Nilsson L. and *Rybo G* Acta Obst. et Gynec. Scand. 44 467 1965

– Obstetrik och gynekologi 3 243 1966

Okamoto S and *Okamoto U* Keio J Med 11 105, 1962

Oshiba S and *Okamoto S* Keio J Med. 11 117 1962

Received on Feb 24th, 1967

Forsberg, John-Gunnar and Ingemanson, Carl-Axel, Acta obst. et gynec. scandinav. 46, 581 1967

From the Department of *Anatomy* and the *Tornblad* Institute for Comparative Embryology *(Prof Bengt Källén)*, and the *Department of* Obstetrics and Gynaecology *(Prof A. Sjövall)* University *of Lund Sweden*

SUCCESSFUL GROWTH OF HUMAN COLUMNAR CERVICAL EPITHELIUM GRAFTED INTO NEONATAL RATS

BY

JOHN-GUNNAR FORSBERG AND CARL-AXEL INGEMANSON

Several studies have been devoted to the tissue culture of normal cervical epithelium (e.g *Mellgren et al.* 1962 *Richart* 1964 a, 1964 b *Richart* and *Lerch* 1966 *Auersperg* and *Worth* 1966) In these cell culture studies, interest has been mainly focused on the growth behaviour and characteristics of the epithelium and on this compared with that of abnormal cervical epithelium. The same object has been pursued also when normal portio epithelium has been cultured in the cheek-pouch of cortisone treated hamsters (*Mellgren et al.* 1962) Other studies have been devoted to analyses of the thymidine-H^3 cytidine-H^3 leucine-H^3 and cystine-S^{35} uptake in short-term incubations of cervical epithelium (*Reid* 1964 a *Fettig et al.* 1964 a, 1964 b, 1966) and the sperm penetration through columnar and metaplastic epithelium in *in vitro* cultures for 15–24 hours (*Reid* 1964 b) Biochemical studies have been carried out on normal cervical tissue cultured for 72 hours in a synthetic medium (*Mainigi et al.* 1965) No histological studies were made to establish the appearance of the tissue after the culture period.

It has not been possible to find any report in the literature on organ culture of human columnar cervical epithelium with a definite preservation of histological structure for a longer period than 24 hours.

In the course of an investigation on different aspects of metaplastic changes in the human uterine cervix, we wanted a

method of keeping the columnar epithelium in culture for considerably longer periods than one day. Several trials with organ cultures *in vitro* under several different conditions failed to ensure an acceptable survival and growth of the epithelium nor did the cheek-pouch in cortisone treated hamsters offer a suitable milieu. For these reasons we tried to graft the columnar epithelium into neonatal rats. This paper reports the successful growth of such grafts for periods of 10–14 days.

Material and methods

The cervical epithelium used in this investigation was taken at curettage from the endocervix. All patients were within the fertile age group except one in the menopause. Curettage was carried out in all cases on account of irregular bleeding. Before operation vagina and portio were washed with an antiseptic.

One part of the epithelial material received at the curettage in the following called "original preparation" was fixed in Bouin's fluid, paraffin embedded sectioned and stained in haematoxylin and eosin. This was done to ascertain the appearance of the epithelium and to discard from further study preparations with pathological changes such as e.g. cervicitis. Another part of the material was used for transplantation. To ensure that the appearance of the original preparation was as representative as possible of the transplanted material the former was taken from the same small tissue piece as that used for transplantation.

The transplantations were made into neonatal Sprague-Dawley rats on the first day of life usually within 12 hours after birth. The host females were anaesthetized by being put on ice. Thereafter they were put under a dissecting microscope and a small incision was made into the skin and muscles anterior to the femur (only the one side was operated upon). A small endocervical tissue piece was put into the muscle and the incision was closed by a suture 7–0 silk on a 3/8 circle taper. The skin incision was also closed by sutures. The operation did not cause any bleeding. After the operation, the animals were warmed for a short time under an electric light until they showed spontaneous movements.

Table I.

Preparation Number	The Grafts Studied after Days	Survival
Ce 13		+ + +
14	10	+ + +
15		+ +
Ce 140	11	died
141		+ + +
Ce 17		died
18		+ +
19		+
20	12	+ + +
21		+ +
129		+ + +
135		+ + +
Ce 64		+ + +
65		+ + +
84	13	+ + +
151		+ + +
153		+ + +
Ce 75		+ +
92		+ + +
93		+ +
104		+ +
106		+ +
115	14	+ +
116		+ +
132		+ +
138		+ + +
144		died
145		
146		
147		+
155		+ + +

These preparations were taken from the same patient.

method of keeping the columnar epithelium in culture for considerably longer periods than one day Several trials with organ cultures *in vitro* under several different conditions failed to ensure an acceptable survival and growth of the epithelium nor did the cheek-pouch in cortisone treated hamsters offer a suitable milieu. For these reasons we tried to graft the columnar epithelium into neonatal rats. This paper reports the successful growth of such grafts for periods of 10–14 days.

Material and methods

The cervical epithelium used in this investigation was taken at curettage from the endocervix. All patients were within the fertile age group except one in the menopause Curettage was carried out in all cases on account of irregular bleeding. Before operation, vagina and portio were washed with an antiseptic.

One part of the epithelial material received at the curettage, in the following called original preparation was fixed in Bouin s fluid, paraffin embedded sectioned and stained in haematoxylin and eosin. This was done to ascertain the appearance of the epithelium and to discard from further study preparations with pathological changes such as e g cervicitis. Another part of the material was used for transplantation To ensure that the appearance of the original preparation was as representative as possible of the transplanted material the former was taken from the same small tissue piece as that used for transplantation

The transplantations were made into neonatal Sprague-Dawley rats on the first day of life usually within 12 hours after birth The host females were anaesthetized by being put on ice Thereafter they were put under a dissecting microscope and a small incision was made into the skin and muscles anterior to the femur (only the one side was operated upon) A small endocervical tissue piece was put into the muscle and the incision was closed by a suture 7–0 silk on a 3/8 circle taper The skin incision was also closed by sutures The operation did not cause any bleeding After the operation, the animals were warmed for a short time under an electric light until they showed spontaneous movements.

Table I.

Preparation Number	The Grafts Studied after Days	Survival
Ce 13		+ + +
14	10	+ + +
15		+ +
C 140	11	died
141		+ + +
Ce 17		died
18		+ +
19		+
20	12	+ + +
21		+ +
129		+ + +
135		+ + +
Ce 64		+ + +
65		+ + +
84	13	+ + +
151		+ + +
153		+ + +
Ce 75		+ +
82		+ + +
93		+ +
104		+ +
106		+ +
115	14	+ +
116		+ +
132		+ +
138		+ +
144		+ + +
145		died
146		
147		+
155		+ + +

These preparations were taken from the same patient.

method of keeping the columnar epithelium in culture for considerably longer periods than one day Several trials with organ cultures *in vitro* under several different conditions failed to ensure an acceptable survival and growth of the epithelium nor did the cheek-pouch in cortisone treated hamsters offer a suitable milieu. For these reasons we tried to graft the columnar epithelium into neonatal rats This paper reports the successful growth of such grafts for periods of 10–14 days

Material and methods

The cervical epithelium used in this investigation was taken at curettage from the endocervix. All patients were within the fertile age group except one in the menopause. Curettage was carried out in all cases on account of irregular bleeding. Before operation vagina and portio were washed with an antiseptic

One part of the epithelial material received at the curettage in the following called original preparation" was fixed in Bouin s fluid paraffin embedded, sectioned and stained in haematoxylin and eosin This was done to ascertain the appearance of the epithelium and to discard from further study preparations with pathological changes such as e g cervicitis Another part of the material was used for transplantation. To ensure that the appearance of the original preparation was as representative as possible of the transplanted material the former was taken from the same small tissue piece as that used for transplantation.

The transplantations were made into neonatal Sprague-Dawley rats on the first day of life usually within 12 hours after birth. The host females were anaesthetized by being put on ice Thereafter they were put under a dissecting microscope and a small incision was made into the skin and muscles anterior to the femur (only the one side was operated upon) A small endocervical tissue piece was put into the muscle and the incision was closed by a suture 7–0 silk on a 3/8 circle taper The skin incision was also closed by sutures The operation did not cause any bleeding After the operation, the animals were warmed for a short time under an electric light until they showed spontaneous movements.

Table I.

Preparation Number	The Grafts Studied after Days	Survival
Ce 13		+ + +
14	10	+ + +
15		+ +
Ce 140	11	died
141		+ + +
Ce 17		died
18		+ +
19		+
20	12	+ + +
21		+ +
129		+ + +
133		+ + +
Ce 64		+ + +
65		+ + +
84	13	+ + +
151		+ + +
153		+ + +
Ce 75		+ +
92		+ + +
93		+ +
104		+ +
106		+ +
115	14	+ +
116		+ +
132		+ +
138		+ + +
144		died
145		
146		
147		+
155		+ +

These preparations were taken from the same patient



Fig. 1 A. The appearance of the original preparation of the graft Ce 64

In all 31 transplantations were made into 31 host animals The grafts were taken from 16 different patients The survival of the operated young was 100 % Only in exceptional cases infection was seen in the wounds The grafts in these animals were excluded from the final analysis

On the 3rd day after operation, the animals were given 0.5 mg cortisone acetate injected subcutaneously

The grafts were allowed to grow for 10–14 days (see Table I) The host animals were then killed by decapitation and the thigh muscle containing the graft was fixed in Bouin s fluid, dehydrated in alcohol, paraffin embedded, and serially sectioned with a section thickness of 5 microns The sections were stained in haematoxylin and eosin.

Results

The cortisone injection caused a growth retardation of the animals and a pronounced loss of subcutaneous fat. The development of the skin hair was impaired.

The survival of the grafts is shown in Table I The survival is indicated with one two or three pluses Three pluses indicate grafts with a high columnar epithelium of the type shown in Fig 1 No signs of degeneration are seen in either the epithelium



Fig. 1 B. The graft after 13 days survival in rat muscle. Still high columnar epithelium. Magnification A and B appr. 90 ×

or the surrounding stroma, nor is there any infiltration by round cells or granulocytes. The similarity between the epithelium in these grafts and that in the original preparations is striking (Fig. 1). Grafts with this appearance were found also after the longest growth time 14 days.

Two pluses also indicate a good survival without degeneration in either epithelium or stroma, nor any leukocytic infiltration. The characteristic trend in these cases is that the epithelium is distinctly lower than in the original preparations and than in the three-plus grafts. Sometimes, the grafts form a cyst whose epithelial wall seems to have been stretched: the height of the epithelium is low and often the cells are flattened (Fig. 2).

The grafts whose survival is characterized by one plus showed some degeneration in the epithelium or in the stroma. Finally five grafts were completely necrotic.

In the epithelium of those grafts showing a good survival (two

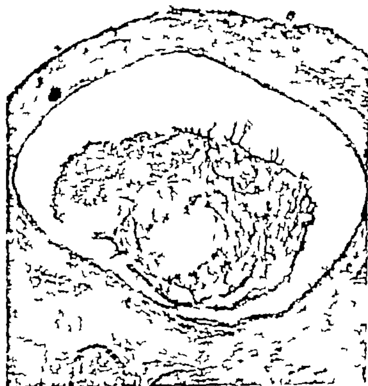


Fig. 2 A. Example of cyst formation in the graft Ce 75 14 days surviv Secretory material in the lumen.



Fig 2 B. Detail of the wall of the cyst pictured in Fig 2 A. Note the occu rence of mitosis. Magnification A appr 90 × B appr 560 ×



Fig. 3 Detail of the epithelium in the graft Ce 84 after 13 days in rat muscle. T the left, columnar epithelium with reserv cells to the right, a metaplastic epithelium. Magnification appr. 220 ×

and three pluses) several scattered mitoses can be seen. This is taken as a sign not only of survival but of growth in the grafts.

The original preparation from one of the patients (grafts Ce 104 106) showed a metaplastic epithelium the same type of epithelium also appeared in the grafts after 14 days. The original preparation for graft Ce 84 showed a fine columnar cervical epithelium with a layer of reserve cells In the graft, there is both a columnar epithelium with reserve cells and regions with a metaplastic epithelium (Fig. 3) However this does not mean that the metaplasia must have occurred during the growth of the graft, but may instead point to the difficulty of getting the original preparation representative of the graft.

Discussion

Preliminary trials showed that intramuscular grafts of human endocervical epithelium into normal, untreated, newborn rats

were usually necrotic after 10 days We then tried to achieve prolonged survival by combining the transplantation with thymectomy of the newborn rats as thymectomy soon after birth is known to inhibit the homograft reaction and to allow mice to accept even rat skin heterografts (e g *Burnet* 1962 *Miller* 1964 a b) *It has been reported (Martinez et al 1962) that an* increased survival of skin homografts after neonatal thymectomy should take place only in mice strains isogeneic at the H 2 histocompatibility locus but homologous with respect to other weaker loci. This was later shown to be due to minute residual thymus tissue and a complete thymectomy resulted in the acceptance of skin homografts even across strong antigenic barriers (*Good et al* 1962) Against this background, it is difficult to explain our failure to get a prolonged survival of the cervical epithelium in neonatally thymectomized rats. Most of the grafts showed degenerative changes when studied after 10 days, in spite of a *macroscopically complete thymectomy Nor did the grafts survive* when transplanted to the cheek pouch of cortisone treated hamsters in which milieu normal portio epithelium grows well (*Mellgren et al* 1962)

The results described in this investigation suggest that the thigh muscles of cortisone treated neonatal rats afford a suitable milieu for the survival and growth of grafts of human endocervical epithelium. Many of the grafts showed an epithelium almost identical with that of the original preparations others were transformed into thin-walled cysts. The latter type of grafts were especially numerous in the group studied after 14 days. The cyst *formation does not represent any degenerative* changes as the cyst wall had a healthy epithelium, often with mitoses the cysts seem, instead to have arisen through an enclosing of secretory products from the epithelium.

Thus the cortisone treatment has had an important influence on prolonging survival. Besides inhibiting immune reactions (see *Berenbaum* 1965 *Elves* 1966) it is also possible that cortisone in our system has a direct influence on the cervical epithelium. Concerning immunological conditions newborn rats are in a poor state of immunological responsiveness (e g *Southam et al.* 1966) The animals become able to develop immunity within the first

two weeks after birth (*Woodruff* and *Simpson* 1955) This has been utilized when injecting fetal and newborn animals with cell suspensions in order to get immunological tolerance to skin grafts later in life (*Woodruff* and *Simpson* 1955 *Billingham et al* 1955–1956 *Billingham* and *Brent* 1958–1960) By intravenous injections of cell suspensions into neonatal rats, other authors have been able to induce tolerance to human cells (*Southam et al.* 1964) and even to human tumours transplanted later (*Southam et al.*, 1966) The median survival time of skin homografts in adult non-tolerant rats and mice is about 10–11 days (*Billingham et al.* 1954 1965) Inter-strain skin grafts to neonatal mice show a longer survival time degenerative changes begin on the 16th or 17th day and are complete at 21 days and no tolerance is induced. Even if it is easier to induce tolerance in neonatal rats than in neonatal mice (*Woodruff* and *Simpson* 1955 *Billingham et al* 1955–1956 *Billingham* and *Brent* 1958–1960) our results are too short-term to allow the conclusion that tolerance for the cervical epithelium has been induced. Because of the cyst formation the grafts do not seem suitable for study after periods longer than about two weeks. During this time however the muscle milieu is appropriate for survival and growth under cortisone treatment.

SUMMARY

Human endocervical epithelium taken from patients at curettage was transplanted into the thigh muscles of rat young on their first day of life On the third day after the operation, the young were given an injection of cortisone acetate The grafts survived well for 10–14 days and showed mitoses in the epithelium. In some cases cysts were formed with secretory material in the lumen

Acknowledgement

This investigation was supported by grants from the Swedish Cancer Society (No 67 46) and from the Swedish Research Council (No. 12X 579-03)

were usually necrotic after 10 days We then tried to achieve *prolonged survival* by combining the transplantation with thymectomy of the newborn rats as thymectomy soon after birth is known to inhibit the homograft reaction and to allow mice to accept even rat skin heterografts (e g *Burnet* 1962 *Miller* 1964 a, b) It has been reported (*Martinez et al.* 1962) that an increased survival of skin homografts after neonatal thymectomy should take place only in mice strains isogeneic at the H 2 histocompatibility locus but homologous with respect to other weaker loci This was later shown to be due to minute residual thymus tissue, and a complete thymectomy resulted in the acceptance of skin homografts even across strong antigenic barriers (*Good et al* 1962) Against this background, it is difficult to explain our failure to get a prolonged survival of the cervical epithelium in neonatally thymectomized rats. Most of the grafts showed degenerative changes when studied after 10 days in spite of a macroscopically complete thymectomy Nor did the grafts survive when transplanted to the cheek pouch of cortisone treated hamsters, in which milieu normal portio epithelium grows well (*Mellgren et al*, 1962)

The results described in this investigation suggest that the thigh muscles of cortisone treated neonatal rats afford a suitable milieu for the survival and growth of grafts of human endocervical epithelium. Many of the grafts showed an epithelium almost identical with that of the original preparations others were transformed into thin walled cysts The latter type of grafts were especially numerous in the group studied after 14 days. The cyst formation does not represent any degenerative changes as the cyst wall had a healthy epithelium, often with mitoses the cysts seem instead, to have arisen through an enclosing of secretory products from the epithelium.

Thus, the cortisone treatment has had an important influence on prolonging survival. Besides inhibiting immune reactions (see *Berenbaum* 1965 *Elves* 1966) it is also possible that cortisone in our system has a direct influence on the cervical epithelium. Concerning immunological conditions newborn rats are in a poor state of immunological responsiveness (*e g Southam et al* 1966) The animals become able to develop immunity within the first

Boe Finn, Acta obst et gynec scandinav 46 391 1967
From the Department of Obstetrics and Gynecology (Finn Boe M.D.)
Aker Hospital Oslo Norway

STUDIES ON THE HUMAN PLACENTA

I. The Cell Islands in the Young Placenta

BY

FINN BOE

Introduction

The peripheral cytotrophoblast (*Wislocki* and *Bennett* 1943) comprises the trophoblastic cell columns the cell islands and the trophoblastic shell. The latter is transformed into a basal plate contiguous to *decidua basalis* and placental septa. The peripheral cytotrophoblastic cells are chromophilic and differ in several important respects from the chromophobic Langhans cells of the chorionic villi (*Wislocki* 1951)

The histology of the cell islands has been thoroughly described by *Stieve* (1940) *Wislocki* and *Bennett* (1943) *Ortmann* (1955) among others. The mentioned and previous authors considered the islands to be of fetal origin.—Recent studies, however are in favour of a maternal genesis the cell islands are formed on the basis of disrupted cell clusters from the *decidua basalis* conveyed by the blood stream to all areas of the intervillous space (*Hormann* and *Lemtis* 1965) The islands increase in size by deposition of fibrinoid material, penetrated fetal elements may also be transformed into fibrinoid. Recent studies on sex chromatin determinations by *Klinger* and *Ludwig* (1957) speak in favour of a maternal genesis.

Many students in the field have emphasized the histological resemblance between the basal plate the placental septa and the cell islands *Wislocki* and *Bennett* (1943) *Latta* and *Beber* (1953) *Ortmann* (1955) and *Thomsen* and *Willemsen* (1959)

REFERENCES

Auersperg, N and *Worth A.* Int. J Cancer 1 219 1966
Berenbaum M C. Brit. Med Bull. 21 140, 1965
Billingham R. E. and *Brent L.* Phil. Trans. Roy Soc B 242 439 1958–1960
Billingham R. E. Brent L. and *Medawar P B.* Proc. Roy Soc. B 143 58, 1954
– Phil. Trans. Roy Soc. B 239 357 1955–1956
Billingham R. E. Defendi V Silvers W K. and *Steinmuller D* J Nat. Cancer Instit. 28 365 1965
Burnet M F Brit. Med. J II 807 1962
Elves M W The lymphocytes Lloyd-Lake Ltd. London 1966
Fettig, O and *Oehlert W* Arch. Gynäk. 199 649 1964 a
– Verh. Dtsch Gesellschaft f Path 48 Tagung p 288 1964 b
Fettig, O and *Sievers R.* Beitr path. Anat. 133 83 1966
Good R. A. Dalmasson A. P Martinez C Archer O K. Pierce J C and *Papermaster B W* J exp. Med 116 773 1962
Mainigi K. D Rajalakshmi R. Ramakrishnan C. V Patel V G and *Patel T V* Oncologia 19 67 1965
Martinez C. Kersey J., Papermaster B W and *Good R. A.* Proc. Soc. exp. Biol. Med. 109 193 1962
Mellgren J Boeryd B., and *Hagman M* Cancer Res. 22 139 1962
Miller J F A. P Brit. Med. Bull. 21 111 1964 a
– Science 144 1544 1964 b
Reid B L. J Nat. Cancer Instit. 32 1059 1964 a
– Lancet I 21 1964 b
Richart R. M Am. J Obstet. Gynec 88 710 1964 a
– Cancer Res. 24 662, 1964 b
Richart R. M and *Lerch V* J Nat. Cancer Instit. 37 317 1966
Southam C M Babcock V and *De Mad M* Cancer Res. 24 345 1964
Southam C M Tan i A. F and *Ross S L* Cancer 19 1670 1966
Woodruff W F A. and *Simpson L O* Brit. J exp Path. 36 494 1955

Received on Dec. 12th 1966

them closely to their rise from the chorionic plate, and removing them bluntly with their attached complex of villi. The dissection is continued with dissection needles till it is possible to inspect the individual villi and their communicatons.—Placentae depleted of blood, may be fixed immediately after delivery and examination postponed until convenient.—Placental tissue removed by curettage may be subjected to examination by the same technique.

Fixation in formol 4 %

Staining methods

1 Haematoxylin Eosin (HE)
2 Lendrum s Picro Mallory method
3 Mallory s Trichrome stain
4 Masson s Trichrome stain
5 Silver Impregnation (Fontana) (SIF)
6 Mallory s Phospho Tungstic Acid Haematoxylin stain (PTAH)

A series of sections were cut from each specimen The material was supplied with conventional histological sections from the same placentae. The following methods proved most appropriate for the staining of fibrinoid Lendrum, Masson and PTAH.

1 GROSS ANATOMY OF THE CELL ISLANDS

With the above mentioned simple dissection technique the cell islands are easily visible and not difficult to remove. As a rule, they are globular formations dispersed among the villi, most numerous toward the basal plate, but they occur in the vicinity of the chorionic plate as well. In addition to the basal plate the villi attach to these islands, usually by syncytial bands of various length, more seldom directly The frequency of their occurrence aries considerably from placenta to placenta.

Characteristic of these formations are their highly different translucency In transillumination all transitions are found, from light (Fig 1) to dark (Fig. 2) opaque almost black. Obviously a successi ely increased formation of opaque substance occurs till the whole i land is filled with opaque substance. The ap-

considered these structures to be producers of chorionic gonadotrophin.

The constant occurrence of the cell islands indicates a physiological function So far such a function is not ascertained. The present study intends to make a contribution on

(1) the formation of the cell islands

(2) the relationship of fibrinoid to the cell islands.

The fetal placenta is nourished from the maternal blood and this fact is unique the structures derived from the trophoblast are nourished from a biologically and genetically different individuum Anabolic and catabolic processes are involved, proceeding simultaneously A hypothesis will be presented concerning the possible role of fibrinoid in the catabolic processes of the placental metabolism.

Material and Technique

Fresh untreated placental tissue from therapeutic abortions was used, removed by minor Caesarean section. Immediately after delivery the placenta was placed in tepid saline solution. The umbilical cord was cut about 3 cm from its insertion and the blood forced out by repeated careful pressure

For the dissection was used a method similar to a previously described one (*Boe* 1953) which may be called selective dissection the tissue was dissected in transillumination under stereo microscope (Zeiss Opton) usually at $\times 10$ magnification. The chorionic plate was split radially thereafter circumcized over the piece of tissue selected for examination, about 3×3 cm proved convenient. The selected piece was removed bluntly from the adjacent tissue and transferred to a Petri dish in which the dissection was carried out with the tissue immersed in water In water the fetal structures become suspended, which greatly improves the exposure and facilitates dissection. During the dissection specimens required for histological examination are removed and directly transferred into fixation fluid.

The principle of this dissection is the removal of the individual stems from the selected piece of tissue by successively cutting

them closely to their rise from the chorionic plate, and removing them bluntly with their attached complex of villi. The dissection is continued with dissection needles till it is possible to inspect the individual villi and their communications.—Placentae, depleted of blood, may be fixed immediately after delivery and examination postponed until convenient.—Placental tissue removed by curettage may be subjected to examination by the same technique.

Fixation in formol 4 %

Staining methods

1. Haematoxylin Eosin (HE)
2. Lendrum s Picro Mallory method
3. Mallory s Trichrome stain
4. Masson s Trichrome stain
5. Silver Impregnation (Fontana) (SIF)
6. Mallory's Phospho Tungstic Acid Haematoxylin stain (PTAH)

A series of sections were cut from each specimen. The material was supplied with conventional histological sections from the same placentae. The following methods proved most appropriate for the staining of fibrinoid Lendrum Masson and PTAH.

I GROSS ANATOMY OF THE CELL ISLANDS

With the above mentioned simple dissection technique the cell islands are easily visible and not difficult to remove. As a rule, they are globular formations dispersed among the villi, most numerous toward the basal plate but they occur in the vicinity of the chorionic plate as well. In addition to the basal plate, the villi attach to these islands, usually by syncytial bands of various length, more seldom directly. The frequency of their occurrence varies considerably from placenta to placenta.

Characteristic of these formations are their highly different translucency. In transillumination all transitions are found, from light (Fig. 1) to dark (Fig. 2) opaque almost black. Obviously a successively increased formation of opaque substance occurs, till the whole island is filled with opaque substance. The ap-

considered these structures to be producers of chorionic gonadotrophin.

The constant occurrence of the cell islands indicates a physiological function. So far such a function is not ascertained. The present study intends to make a contribution on
(1) the formation of the cell islands,
(2) the relationship of fibrinoid to the cell islands.

The fetal placenta is nourished from the maternal blood and this fact is unique the structures derived from the trophoblast are nourished from a biologically and genetically different individuum Anabolic and catabolic processes are involved, proceeding simultaneously A hypothesis will be presented concerning the possible role of fibrinoid in the catabolic processes of the placental metabolism.

Material and Technique

Fresh untreated placental tissue from therapeutic abortions was used, removed by minor Caesarean section. Immediately after delivery the placenta was placed in tepid saline solution. The umbilical cord was cut about 3 cm from its insertion and the blood forced out by repeated careful pressure

For the dissection was used a method similar to a previously described one (*Boe* 1953) which may be called selective dissection the tissue was dissected in transillumination under stereo microscope (Zeiss Opton) usually at ×10 magnification. The chorionic plate was split radially thereafter circumcized over the piece of tissue selected for examination, about 3×3 cm proved convenient The selected piece was removed bluntly from the adjacent tissue and transferred to a Petri dish in which the dissection was carried out with the tissue immersed in water In water the fetal structures become suspended, which greatly improves the exposure and facilitates dissection. During the dissection specimens required for histological examination are removed and directly transferred into fixation fluid.

The principle of this dissection is the removal of the individual stems from the selected piece of tissue, by successively cutting

them closely to their rise from the chorionic plate and removing them bluntly with their attached complex of villi The dissection is continued with dissection needles till it is possible to inspect the individual villi and their communications.—Placentae depleted of blood, may be fixed immediately after delivery and examination postponed until convenient.—Placental tissue removed by curettage may be subjected to examination by the same technique.

Fixation in formol 4 %

Staining methods

1 Haematoxylin Eosin (HE)
2 Lendrum s Picro Mallory method
3 Mallory s Trichrome stain
4 Masson s Trichrome stain
5. Silver Impregnation (Fontana) (SIF)
6. Mallory s Phospho Tungstic Acid Haematoxylin stain (PTAH)

A series of sections were cut from each specimen. The material was supplied with conventional histological sections from the same placentae The following methods proved most appropriate for the staining of fibrinoid Lendrum, Masson and PTAH.

1 GROSS ANATOMY OF THE CELL ISLANDS

With the above mentioned simple dissection technique the cell islands are easily visible and not difficult to remove. As a rule, they are globular formations dispersed among the villi, most numerous toward the basal plate, but they occur in the vicinity of the chorionic plate as well. In addition to the basal plate, the villi attach to these islands, usually by syncytial bands of various length more seldom directly The frequency of their occurrence varies considerably from placenta to placenta.

Characteristic of these formations are their highly different translucency In transillumination all transitions are found, from light (Fig. 1) to dark (Fig. 2) opaque almost black. Obviously successively increased formation of opaque substance occurs, till the whole island is filled with opaque substance. The ap-



Fig. 1 Moderate opaque cell island Untreated preparation Transillumination.



Fig 2. Highly opaque cell island Untr ted preparation Transillumination The cell islands Figs 1 and were removed from the same placenta (10 weeks) The photographs were taken consecuti ely identical lumination and magnifi ation.

pearance may resemble coagulated protein and biochemical evidence (unpublished) may support that the opaque substance is insoluble protein. The present histological study is based upon the gross appearance of the cell islands according to their degree of opacity

II HISTOLOGY

A. *Formation of the Cell Islands*

The primary histological change seems to be a mighty *proliferation* of cytotrophoblastic cells originating from a limited area (segment) in a villus. The cluster of cells is directed towards the intervillous space (IVS) usually from two or more villi simultaneously The cell clusters are growing towards a common centre (Plate I A) During the growth the syncytiotrophoblast (syncytium) can be observed bordering the clusters like an unbroken band (Plate I B)

At a certain moment during the growth an *eruption* of cytotrophoblastic cells occurs, columns of cells from several villi fuse, while forming a cell island (Plate I C) During this process the IVS in the area of the island becomes obliterated. Obviously before eruption and confluence can take place, the syncytial cover has to rupture and the disrupted parts be moved aside during the eruption. And this, actually is what happens (Plate I D) The eruptions occur from very limited areas in the proliferating cell clusters (Plate I E) In these eruptions the nuclei are definitely less closely packed than in the cell clusters whereby the cytoplasm is more easily discerned. This forms a delicate meshwork where the nuclei occur in the knots.

As the result of the eruptions, the mass of cytotrophoblast will appear outside the villous syncytium (Plate I E, among them) This apparently paradoxical finding results from the fusing of two eruptions from the same cell cluster above the intermediate unbroken syncytium (Fig. 3) This finding misled Stieve (1940) to the conclusion that syncytium became transformed into cytotrophoblast.



Fig. 1 Moderate opaque cell island. Untreated preparation. Transillumination.



Fig. 2 Highly opaque cell island. Untreated preparation. Transillumination. The cell islands Figs. 1 and 2 were removed from the same placenta (10 weeks). The photographs were taken consecutively, identical illumination and magnification.

pearance may resemble coagulated protein and biochemical evidence (unpublished) may support that the opaque substance is insoluble protein. The present histological study is based upon the gross appearance of the cell islands according to their degree of opacity

II HISTOLOGY

A. *Formation of the Cell Islands*

The primary histological change seems to be a mighty *prolifera-tion* of cytotrophoblastic cells originating from a limited area (segment) in a villus. The cluster of cells is directed towards the intervillous space (IVS) usually from two or more villi simultaneously The cell clusters are growing towards a common centre (Plate I A) During the growth the syncytiotrophoblast (syncytium) can be observed bordering the clusters like an unbroken band (Plate I B)

At a certain moment during the growth an *eruption* of cytotrophoblastic cells occurs, columns of cells from several villi fuse, while forming a cell island (Plate I C) During this process the IVS in the area of the island becomes obliterated. Obviously before eruption and confluence can take place the syncytial cover has to rupture and the disrupted parts be moved aside during the eruption And this actually is what happens (Plate I D) The eruptions occur from very limited areas in the proliferating cell clusters (Plate I E) In these eruptions the nuclei are definitely less closely packed than in the cell clusters, whereby the cytoplasm is more easily discerned This forms a delicat meshwork where the nuclei occur in the knots.

As the result of the eruptions the mass of cytotrophoblast will appear outside the villous syncytium (Plate I E, among other) This apparently paradoxical finding results from the fu ing of two eruptions from the same cell cluster above the intermediat unbroken syncythm (Fig. 3) This finding misled Stieve (1940) to the conclusion that syncytium became transformed into cytotrophoblast.



Fig. 1. Moderate opaque cell island. Untreated preparation. Transillumination.



Fig. 2. Highly opaque cell island. Untreated preparation. Transillumination. The cell islands Figs. 1 and 2 were removed from the same placenta (10 weeks). The photographs were taken consecutivel dentical illumination and magnification.







A. Cell clusters of cytotrophoblast in a group of villi. 10 weeks. Conv HE x80

B: Detail of A, x800: Unbroken syncytium bordering cell clusters.

C: Formation of a cell island by eruptions of cytotrophoblastic cells from the cell clusters. IVS not completely obliterated (centre). Villus below extreme left, does not participate in formation (detail Plate I D). Centre, extreme left: transition of normal syncytium (deep violet) into fibrinoid (pink). Fragments of syncytium (multinucleated) inside the area of cell island. No fibrinoid inside the area. 10 weeks. Conv HE x80







D: Detail of C, x800: Syncytium ruptured, fragments of disrupted syncytium expelled into IVS (note connection with mother tissue). Incipient eruption of cytrophoblast (centre).

E. Cell island. Two eruptions arising from limited areas in cell cluster (compare Fig. 3). Fragments of syncytium. Centre below fibrinoid. 8 weeks. HE x200

F. Cell island. Moderate amount of fibrinoid, brilliantly red. Villous mesenchyma (green) penetrating into centre of island. 8 weeks. Masson x200

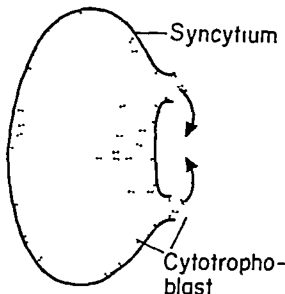


Fig. 3. Two columns of cytotrophoblastic cells fuse (arrows) resulting in a mass of cytotrophoblast outside the syncytium.

B Regressive Changes in the Cell Islands

The described (newly formed) island, presumably will appear translucent in transillumination. The change from translucency via light to dark opaque exhibits a series of histological changes in each of the three villous tissue elements i e cytotrophoblast, syncytium and mesenchyma. The histological material tends to show a parallel course between increasing opacity and gradual transformation of the cell islands into fibrinoid. The highly opaque islands appear practically structureless merely fragments of tissue elements can be discerned in the mass of fibrinoid. Presumably fibrinoid is the substance which appears opaque in transillumination.

During the formation of fibrinoid the cytoplasm of the *cytotrophoblast* swells the fibrils grow coarser until fusing into a plaque of amorphous substance During this development a characteristic change of colour occurs in the Masson method from light redbrown to brilliant red (Plates I F and II D) in Lendrum from dark lilac to scarlet red (Plate II A and E) or deep blue (Plate II B) and in PTAH from violet to intensive







A. Cell clusters of cytotrophoblast in a group of villi. 10 weeks. Conv HE x80

B: Detail of A, x800: Unbroken syncytium bordering cell clusters.

C: Formation of a cell island by eruptions of cytotrophoblastic cells from the cell clusters. IVS not completely obliterated (centre). Villus below extreme left, does not participate in formation (detail Plate I D). Centre, extreme left: transition of normal syncytium (deep violet) into fibrinoid (pink). Fragments of syncytium (multinucleated) inside the area of cell island. No fibrinoid inside the area.
10 weeks. Conv HE x80







D: Detail of C, x800: Syncytium ruptured, fragments of disrupted syncytium expelled into IVS (note connection with mother tissue). Incipient eruption of cytrophoblast (centre).

E. Cell island. Two eruptions arising from limited areas in cell cluster (compare Fig. 3). Fragments of syncytium. Centre below: fibrinoid.
8 weeks. HE x200

F: Cell island. Moderate amount of fibrinoid, brilliantly red. Villous mesenchyma (green) penetrating into centre of island.
8 weeks. Masson x200

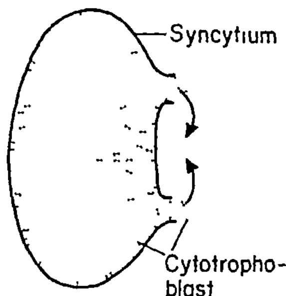
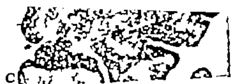


Fig. 3 Two columns of cytotrophoblastic cells fuse (arrows) resulting in a mass of cytotrophoblast outside the syncytium.

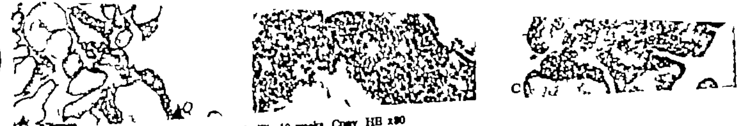
B Regressive Changes in the Cell Islands

The described (newly formed) island presumably will appear translucent in transillumination. The change from translucency *via* light, to dark opaque exhibits a series of histological changes in each of the three villous tissue elements *i. e* cytotrophoblast, syncytium and mesenchyma. The histological material tends to show a parallel course between increasing opacity and gradual transformation of the cell islands into fibrinoid. The highly opaque islands appear practically structureless merely fragments of tissue elements can be discerned in the mass of fibrinoid. Presumably fibrinoid is the substance which appears opaque in transillumination.

During the formation of fibrinoid the cytoplasm of the *cytotrophoblast* swells the fibrils grow coarser until fusing into a plaque of amorphous substance During this development a characteristic change of colour occurs in the Masson method from light redbrown to brilliant red (Plates I F and II D) in Lendrum from dark lilac to scarlet red (Plate II A and E) or deep blue (Plate II B) and in PTAH from violet to intensive







A. Cell clusters of cytotrophoblast in a group of villi. 10 weeks. Conv HE x80

B: Detail of A, 300: Unbroken syncytium bordering cell clusters.

C: Formation of cell island by eruptions of cytotrophoblastic cells from the cell clusters. IVS not completely obliterated (centre). Villus below extreme left, does not participate in formation (detail Plate I D). Centre, extreme left: transition of normal syncytium (deep violet) into fibrinoid (pink). Fragments of syncytium (multinucleated) inside the area of cell island. No fibrinoid inside the area. 10 weeks. Conv HE x80







D: Detail of C, x800: Syncytium ruptured, fragments of disrupted syncytium expelled into IVS (note connection with mother tissue). Incipient eruption of cytrophoblast (centre).

E: Cell island. Two eruptions arising from limited areas in cell cluster (compare Fig. 3). Fragments of syncytium. Centre below: fibrinoid. 8 weeks. HE x200

F: Cell island. Moderate amount of fibrinoid, brilliantly red. Villous mesenchyme (green) penetrating into centre of island. 8 weeks. Masson x200





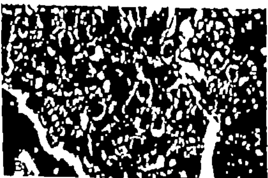


A. Cell island. Moderate amount of fibrinoid scarlet red. 8 weeks. Lendrum x200

B Cell island. Moderate amount of fibrinoid, blue 8 weeks. Lendrum x200

C: Cell island. Advanced changes. Centre. fibrinoid, yellowbrown, with fragments of syncytium. Coarsely fibrillated villous mesenchyma (red) Note abscence of fibrin. 10 weeks. Conv PTAH x200







D· Detail of cell island. Conversion of cytotrophoblastic cytoplasm (redbrown) into fibrinoid (brilliantly red) Thickened nuclear membrane in many nuclei. 10 weeks. Masson x800

E. Detail of cell island. Conversion of cytotrophoblastic cytoplasm (dark lilac) into fibrinoid (scarlet red) 11 weeks. Lendrum x800

F Cell island. Motley appearance. Conversion of cytotrophoblastic cytoplasm (light yellow) into fibrinoid (yellowred to red) Three plaques of embedded naked *mesenchyma (red) with argyrophilic substance (black) One third of mesenchyma in one plaque (left) shrunken 1 to* cluster of argyrophilic substance, lacki g in red stain. 8 weeks. SIF 500





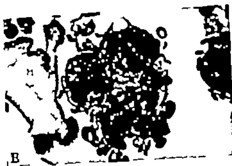


A. Detail of cell island. Conversion of cytotrophoblastic cytoplasm (violet) into fibrinoid (yellowbrown). 9 weeks. PTAH x800

B. Detail of cell island. Abundant decidualike cells dispersed in fibrinoid. Absence of fibrin. 9 weeks. PTAH x800

C. Cell island. Advanced changes. Embedded mesenchyma. 9 weeks. Lendrum x200







D. Cell island. Advanced changes. Embedded mesenchyma. 9 weeks. Masson x200

E. Cell island nearly totally transformed into fibrinoid. Centre: remnants of mesenchyma. 9 weeks. Masson x200

F. Cell island. Structureless central zone (blue) and marginal zone (red). 8 weeks. Lendrum x200

yellowbrown (Plates II C and III A) In the SIF method the cytoplasm appears yellowish, while the nuclei are filled with delicate black granules The fibrinoid is stained yellowred to red (pink) In the nuclei the argyrophilic granules fuse into a black amorphous substance. The fibrinoid thereby assumes a motley appearance (Plate II F)

The syncytium which has been split apart through the cytotrophoblast eruptions, can be observed as bands or multinucleated fragments on the borders of the cell clusters (Plate I E) or inside the area of the cell island (Plate II C) quite unevenly distributed. Superficially these bands, frequently in connection with syncytial bands connecting villi to the islands, may form bizarre configurations. The syncytium likewise becomes transformed into fibrinoid (Plate I C)

In the opaque cell islands villous *mesenchyma* frequently can be observed inside the area of the island, stained green in Masson (Plate I F) In SIF staining the mesenchyma exhibits special features. In the normal villi the mesenchymal tissue consists of cell nuclei, argyrophilic reticular fibers (black) and bundles of collageneous fibers (red) In highly opaque islands changes are observed, from coarse, intensively red stained fibers, to shrunken clusters of argyrophilic substance, the stroma completely lacking in red stain (Plate II F) This staining method proved able to demonstrate remnants of mesenchyma in the form of argyrophilic substance in cases where mesenchyma could not be demonstrated by any other of the applied methods. Mesenchyma inside the area of the islands is rarely covered by epithelium. Most frequently it appears surrounded by a cuff of fibrinoid (transformed syncytium) or naked (Plates I F II F and III C, D and F)

Dispersed in fibrinoid a cell type of characteristic appearance can be demonstrated. In PTAH staining the cell nuclei are big, round and vesicular stained clear blue. The cytoplasm is sharply outlined, intensively dark lilac stained. The shape of the cells is oval not infrequently pointed in either end (Plate III B) These cells are found in the basal plate as well and are in recent literature been considered as decidua cells (*Hörmann* and *Lemtl* 1965 *Hörmann* 1966) Because the cells seem to appear exclusively dispersed in fibrinoid, they may rather be considered

as transformed cytotrophoblastic cells (*Dempsey* and *Wislocki* 1945)

The highly opaque islands appear nearly without structure (Plate III C–F) all elements of cytotrophoblast being transformed into fibrinoid Also in such cases bands and fragments of syncytium may appear superficially or inside the area of the island and naked mesenchyma is a frequent finding (Plate III C and D) In the maximal opaque islands hardly any remnants of villous tissue elements can be traced (Plate III F) In Lendrum staining two areas may appear in contrasting colours a blue central zone and a red marginal zone (Plate III F) —Blood vessels could not be demonstrated in the cell islands.

Discussion

Formation of the cell islands Columns of cytotrophoblastic cells (eruptions) originating from the cell clusters of several villi fuse while forming a cell island In the young placenta villi are attached to the *decidua basalis* by columns of cytotrophoblastic cells (anchoring villi) These columns fuse peripherally forming the cytotrophoblastic shell (Fig 4) The two processes are supposed to be homologous. The multinucleated giant cells, presumably represent syncytium disrupted during this process.

The eruptions are designated primary villi by *Wislocki* and *Bennett* (1943) This term can hardly be justified because the eruptions originate from secondary villi

Relationship of fibrinoid The term placental fibrinoid was introduced by *Hitschmann* and *Lindenthal* (1903) The term is not a favourable one because this substance in the human placenta obviously is not related to the substance of the same name occurring, *e g* in the Aschoff nodules. With Mallory's connective stain, and with azan as well, fibrinoid is coloured blue whereas fibrin stains red (*Grosser* 1925) By histochemical methods likewise fibrinoid appears different from fibrin (*Wislocki* and *Bennett* 1943) However the distinguished American pathologist A T Hertig (*Hellman* and *Hertig*, 1938) suggested that fibrinoid and fibrin are identical substances and this seems



Fig 4 From sagittal section through the uterus and in situ placenta of 5 3-mm embryo At *A*, the terminal portion of coiled artery opens into space within multilayered cytotrophoblastic shell A model prepared from this specimen shows that most of the spaces in the cytotrophoblastic shell are in continuity and that together they form labyrinth, which communicates at intervals (B) with the intervillous space (*IVS*) The inner aspect of the shell is covered by syncytium, and multinucleate giant cells are present in some of the spaces Specimen 8306 section 7 3-2, ×45
From *Harris* and *Ramsey* (1966) Courtesy of the Carnegie Institution of Washington

to be the current view in Anglosaxon (especially in American) literature so far With this opinion *Stieve* (1940) agreed.

Fibrinoid *versus* fibrin has been a matter of much controversy The subject was thoroughly discussed by *Wislocki* and *Bennett* (1943) and, recently by *Boyd* and *Hamilton* (1967) The mentioned authors agree that the two substances are different. This view is corroborated by the following reasons

1 Fibrinoid originates inside the trophoblast and mesenchyma itself representing the final product of all three tissue elements of the villus.

2. Freshly precipitated fibrin must be expected to be deposited *outside* the syncytium. This however, is hardly ever demonstrable.
3. The (presumably) newly formed fibrinoid exhibits an amorphous appearance while fresh fibrin is precipitated as a meshwork of fine threads.
4. In special staining for fibrin (PTAH) fibrin (deep blue) could not be demonstrated in the cell islands in the present study

The described histological changes may be explained as stages in a regressive process. The very formation of the cell islands exhibits characteristic histological features Likewise the further development, characterized by a gradually increasing opacity histologically by a parallel increasing amount of fibrinoid. In the final stage the cell island appears as a structureless mass of fibrinoid. This substance is supposed to represent the final product of all three elements in the chorionic villi *i e* cytotrophoblast syncytium and mesenchyma.

Physiological aspects If the regressive changes are considered as stages in a continual physiological process, this must mean that villi continually are formed and decay In other words, villi in the young placenta must be considered to have a limited span of life In the chorionic tree the leaves incessantly wither while new leaves grow out. The metabolism of the young placenta is high gradually decreasing towards term

It is generally agreed that the fetal placenta is nourished by the maternal blood. Ample evidence supports this view (1) In the young ovum the villi grow prior to the establishment of the fetal circulatory system brilliantly demonstrated by *Hertig* (1935) (2) fetal death does not necessarily cause placental death (3) in hydatidiform mole the placenta develops without a fetus the vessels of the villi lack or are underdeveloped, (4) the vessels of the fetal placenta lack *vasa vasorum* (*Boe* 1953) (5) experimental evidence when the fetuses are removed some time before term the placentae continue to develop *in situ* until term, when they are expelled (*Newton* 1938 *Kirsch* 1938 and *van Wagenen* and *Jenkins* 1939)

Biologically this circumstance is unique the fetal structures

are nourished from a biologically and genetically different individuum, the maternal circulation furnishing the necessary material for growth of the structures and replacement of destroyed tissue (wear and tear") and, further transporting the waste products back to the mother organism from where they are excreted.

The maternal blood will not interfere with the *normal* syncytium lining the walls of the IVS no more than blood will deposit fibrin upon normal endothelium. Because of the extraordinary metabolic situation, it may seem to be a logical necessity that the worn out fetal tissue must be transformed, before the tissue can be split down by the enzyme systems of the maternal blood. This transformed substance is supposed to be fibrinoid.

This concept implies a continuous series of catabolic (regressive) processes, in which the transformation of fetal tissue to fibrinoid enters as a necessary intermediate step As a consequence fibrinoid can not be considered a well defined uniform substance neither in histological nor in biochemical sense

This hypothesis embraces a problem which essentially is a metabolic one. Histologic findings can hardly be expected to give conclusive evidence in a matter of metabolism, but may possibly form the basis of an approach to the problem by biochemistry

SUMMARY

Proliferation of *cytotrophoblastic cells in a limited area* (segment) in a chorionic villus results in the formation of a cell cluster bordered by syncytium.

Rupture of the syncytium occurs in definitely limited areas and columns of cytotrophoblastic cells (eruptions) emerge into the IVS Columns of cells from several villi fuse while forming a cell island, resulting in obliteration of the IVS within the area of the island.

Preliminary presented to the X Northern Congress of Obstetrics and Gynecology Proceedings p 91, Stockholm, 1958

2. Freshly precipitated fibrin must be expected to be deposited *outside* the syncytium This, however is hardly ever demonstrable.
3. The (presumably) newly formed fibrinoid exhibits an amorphous appearance while fresh fibrin is precipitated as a meshwork of fine threads.
4. In special staining for fibrin (PTAH) fibrin (deep blue) could not be demonstrated in the cell islands in the present study

The described histological changes may be explained as stages in a regressive process The very formation of the cell islands *exhibits characteristic histological features Likewise the further* development, characterized by a gradually increasing opacity histologically by a parallel increasing amount of fibrinoid. In the final stage the cell island appears as a structureless mass of fibrinoid. This substance is supposed to represent the final product of all three elements in the chorionic villi *i e* cytotrophoblast syncytium and mesenchyma.

Physiological aspects. If the regressive changes are considered as stages in a continual physiological process this must mean that villi continually are formed and decay In other words villi in the young placenta must be considered to have a limited span of life. *In the chorionic tree the leaves incessantly wither while* new leaves grow out The metabolism of the young placenta is *high gradually decreasing towards term.*

It is generally agreed that the fetal placenta is nourished by the maternal blood. Ample evidence supports this view (1) In the young ovum the villi grow prior to the establishment of the fetal circulatory system brilliantly demonstrated by *Hertig* (1935) (2) fetal death does not necessarily cause placental death (3) in hydatidiform mole the placenta develops without a fetus the vessels of the villi lack, or are underdeveloped, (4) the vessels of the fetal placenta lack *vasa vasorum* (*Boe* 1953) (5) *experimental evidence when the fetuses are removed* some time before term, the placentae continue to develop *in situ until term* when they are expelled (*Newton* 1938 *Kirsch* 1938 and *van Wagenen* and *Jenkins* 1939)

Biologically this circumstance is unique the fetal structures

Newton W. H. Physiol. Rev. 18 419 1938
Ortmann R., Zschr. Anat. Entw.gesch. 119 28 1955
Stieve H. Zschr. mikr.-anat. Forsch. 48 287 1940
Thomsen, K. and Willemsen R. Acta endocrinol. 30 161 1959
van *Wagenen* C. and *Jenkins* R. H. J. Urol. 42 1010 1939
Wislocki, G. B. and *Bennett* H. S. Am. J. Anat. 73 335 1943
Wislocki G. B. Anat. Rec. 109 359 1951

Received on March 31st, 1967

In transillumination the translucency of the cell islands varies from light to dark opaque Histological studies may indicate that the increasing opacity is due to the gradual transformation of the cell island into fibrinoid This transformation comprises all three tissue elements in the villi *i e* cytotrophoblast, syncytium and mesenchyma.—Special staining for fibrin (PTAH) failed to demonstrate this substance in the cell islands

Fibrinoid is supposed to be the result of the catabolic processes *in the fetal metabolism. Transformed into this substance* the fetal tissue can be split down by the enzyme systems of the maternal blood.

Acknowledgements

The Author is deeply indebted to Dr Elizabeth M Ramsey for most valuable advice and helpful criticizm

Fig 3 is drawn by Mrs. Inger Groholt (Department of Anatomy Oslo University)

The histological material was prepared in Dept. of Pathology (head K. A. Larsen M D)

REFERENCES

Boyd J D and *Hamilton W J* J Obstet. Gynaec Brit. Cwlth *74* 161 1967

Boe F Acta obst. gynec. scandinav *32* suppl. 5 1953

Dempsey E. W and *Wislocki G B* Am. J Anat. *76* 277 1945

Grosser O Ztschr Anat. *76* 304 1925

Harris J W S and *Ramsey E M* Contr Embryol. Carneg. Inst No. 260, 38 43 1966

Hellman L. M and *Hertig, A. T* Am. J Path *14* 11 1938

Hertig, A. T Contr Embryol. Carneg. Inst. No 146 *31* 67 1935

Hirschmann J and *Lindenthal O T* Arch Gynäk. *69* 587 1903

Hörmann G and *Lemtis H* Die menschliche Plazenta in Schwalm-Döderlein, Klinik der Frauenheilkunde und Geburtshilfe III 425 1965 Urban u. Schwarzenberg

Hörmann G Ztschr *Geburtsh. Gynäk. 165* 125 *1966*

Kirsch R. E. Am. J Physiol *112* 86 1938

Klinger H P and *Ludwig, K. S* Ztschr Anat Entw gesch. *120* 95 1957

Latta S and *Beber C R.* Science *117* 498 1953

Newton W H Physiol. Rev 18 419 1938
Ortmann R., Zschr Anat. Entw gesch. 119 28, 1955
Stieve H., Zschr mikr.-anat. Forsch. 48 287 1940
Thomsen K. and Willemsen R., Acta endocrinol. 30 161 1959
van Wagenen, C. and Jenkins R. H., J Urol. 42 1010 1939
Wislocki G. B and Bennett H S., Am. J Anat. 73 335 1943
Wislocki G B Anat. Rec. 109 359 1951

Received on March 31st, 1967